ANNUAL REVIEW OF MEDICINE

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# PREFACE

The purpose of these volumes is to review the various fields of medicine regularly. As there is hardly room in a book of comfortable size to cover all the aspects of medicine, and as some of its disciplines scarcely need a yearly review, the more active fields will be considered annually, while other sections will be reviewed only every two or three years. The authors have been asked to make their scope broad and to include their own critical assessment of work discussed. If this interpretation should be biased, a new author for the subject in a succeeding volume is as likely to stress another interpretation and thus in time the whole cycle of attitudes will be voiced. It is our design that the reviews never be expressionless listings containing little more than titles of papers The authors have been urged to pitch their writings at a scholarly level, to include experimental background, and to avoid cookbook therapeutic recitals.

A.B. S.C.M.
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A.M.B. W.C.C
E.M MacK

# TOPICS AND AUTHORS

# ANNUAL REVIEW OF MEDICINE

# VOLUME II (1951)

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# INFECTIOUS DISEASES[1]

By Lowell A. Rantz
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Relatively little of the information which has become available in the last two years dealing with infectious disease in human beings is of interest to the clinician. Several new antimicrobial chemotherapeutic agents have been developed and improved dosage forms of some of the older ones have been introduced. This review will describe in some detail the present status of our knowledge of the antibiotics and will also consider a limited group of topics which recently have been of particular interest to the author. It is realized that many subjects of great actual or potential importance have been omitted, and that many valuable contributions have not been included in the bibliography. Limitations of space and of time forbid any attempt to survey in a comprehensive manner the enormous literature covering all of the aspects of infections in human beings. It is also recognized that valuable papers, dealing with the subjects to be discussed, may have been overlooked. The disappearance of the *Cumulative Index Medicus* as a guide to current literature has compelled the author to include only those reports which came to his attention in the course of a personal survey of medical periodicals.

Consideration of the work of the last few years suggests that medical science has reached a plateau in its understanding of infectious disease and that this is perhaps a suitable time for correlation and recapitulation of knowledge already acquired. This point of view may be reflected in the appearance during the past year of several books of value and importance to physicians regardless of their special interests.

One of these, Dowling's *The Acute Bacterial Diseases (Their Diagnosis and Treatment)* (1), is a splendid summary of the disorders named in the title. Although certain of the sections on therapy have been already outmoded by the development of new antimicrobial agents, it is a volume which should be in the library of every physician and medical student.

Companion volumes, published with the support of the National Foundation for Infantile Paralysis which permits their sale at very reasonable prices, have been edited by members of the Rockefeller Institute One, *Viral and Rickettsial Infections of Man*, edited by Rivers (2), is the first satisfactory compendium of knowledge of these infectious agents and the diseases caused by them The material is presented in a form suitable for study by the medical student or clinician, although the descriptions of the disease processes are not sufficiently comprehensive to permit the exclusive use of this book without correlated reading of other sources. The second text, *Bacterial and Mycotic Infections of Man*, edited by Dubos (3), is also a useful work. This

[1] This review covers the period from approximately July, 1947 to March, 1949

volume has not filled as great a need as the two previous books since many other satisfactory textbooks of bacteriology are available. It can, however, be highly recommended. It may also be of value to bring the monumental *Virus Diseases of Man* by van Rooyen & Rhodes (4) to the attention of physicians. This work is an almost complete review of the literature dealing with the filterable viruses. Its value for reference cannot be overemphasized.

## ANTIMICROBIAL AGENTS

New dosage forms and preparations of older antimicrobial agents have appeared during the last two years, as has considerable information in regard to their mode of action and use in the treatment of disease. In addition, several new antibiotics have reached the stage of clinical trial.

### PENICILLIN

*Mode of action of penicillin.*—Stimulating developments in regard to the mode of action of penicillin and other antibacterial agents have been the result of investigations by Gale in England; these were summarized in the Herter Lectures for 1948 (5). Gale has shown that gram-positive organisms are able to assimilate and retain amino acids within the bacterial cell. Gram-negative organisms, on the contrary, do not assimilate these chemical substances but are able to manufacture them from more simple nitrogenous compounds. In other experiments he demonstrated that sulfonamides and certain other antibacterial agents interfere with the metabolism and utilization of amino acids within the cell Penicillin specifically interferes with the assimilation of the amino acids by gram-positive microorganisms. As *Staphylococcus aureus* was made more and more resistant to the action of penicillin *in vitro* by serial passage in the presence of increasing concentrations of this drug, it required fewer and fewer preformed amino acids in the medium and lost its ability to assimilate these chemicals At very high levels of penicillin resistance, the staphylococcus became morphologically a gram-negative bacillus. The precise manner in which penicillin interferes with the assimilation of amino acids has not been elucidated nor do these observations have practical implications, but they are a long step forward in the understanding of the mode of action of this extremely important antibacterial substance.

*Repository penicillin* —The outstanding advance in the field of penicillin therapy during the year has been the development of the procaine salt of this antibiotic in various menstra for administration by the repository technique It has been known for some time that a mixture of concentrated solutions of penicillin and procaine resulted in the formation of crystals which were identified as the procaine salt of penicillin. Whereas the sodium, potassium and calcium salts are highly soluble in aqueous solutions and body fluids, the procaine salt is not As the result of this physical property, an injection of a suspension of this salt in oil or water results in delayed absorption and the maintenance of prolonged blood and tissue concentrations (6).

This material has been made available commercially in three forms.

In each, 300,000 units of active penicillin are contained in 1 cc. of the injectable substance. In one, the procaine penicillin is suspended in an oil, in another in water, and in the third in oil with 2 per cent aluminum monostearate as a dispersing agent. The type suspended in water is advantageous because the injection of large amounts of oil is avoided. Except for this feature it is not yet clear whether there is any advantage in any one of the three preparations over any other (7 to 12).

It has been stated that the preparation containing aluminum monostearate will maintain very prolonged penicillin blood levels so that injections need be given no more often than every other day (9, 12). The reported data on blood levels following the use of this material are quite persuasive but few clinical reports of the administration of the drug on every other day, or every third day, have appeared. Until such time, it would seem desirable to give at least a daily injection of penicillin in all severely ill patients.

The various preparations of procaine penicillin have been easy to administer. Particularly satisfying has been the exceedingly low incidence of local reactions which were so troublesome when penicillin in oil and wax was used as a repository material Generalized penicillin reactions are, of course, observed from time to time Rather large amounts of procaine are injected but sensitization to this material has not yet been a serious problem.

*Caronamide.*—Interest in caronamide, a substance which blocks the tubular excretion of penicillin, has continued (13 to 16). It has been demonstrated that the administration of this material in adequate amounts will enhance the concentration of plasma penicillin and will prolong the interval of time during which measurable amounts of the drug will be present. Effective dosage is stated to be 24 gm. per day in young persons and 12 gm. per day in persons over 60 years of age. In another section below it is pointed out that the maintenance of continuous plasma and tissue levels of penicillin may not be necessary. Furthermore, the highly satisfactory repository types of procaine penicillin which are now available do maintain continuous plasma levels without the administration of a substance which interferes with kidney function.

There seems to be little place at the present time for caronamide in clinical medicine, since it is a potentially toxic agent and since the final effects of blocking the tubular excretory function for a considerable period of time have not been evaluated. There are doubtless examples of nonhemolytic streptococcus and other types of endocarditis, caused by organisms which are highly resistant to penicillin, in these cases it may be desirable to give caronamide in association with large doses of penicillin. Under these circumstances, it may be wise to use combined antibiotic therapy (see p 9).

*Discontinuous penicillin therapy*—It has been apparent since penicillin was first used in the treatment of infectious disease in human beings that this antibacterial agent need not be present at all times in effective concentrations in the blood and tissues if satisfactory clinical results were to be obtained. Thus Tillett and his associates satisfactorily treated pneumococcus pneu-

monia with four daily injections of relatively small amounts of penicillin (17). Bloomfield and his associates treated and cured a few cases of non-hemolytic streptococcus endocarditis with four and, on one occasion, with only two intramuscular injections of penicillin per day (18). In 1946, Jawetz (19) described experiments involving the treatment of hemolytic streptococcus infection in mice in which he showed that the action of this drug invariably persisted long after measurable concentrations were present in the blood. These observations were subsequently confirmed by White, Lee, & Alverson (20) and by Zubrod (21).

In spite of these observations, nearly all investigations of the use of penicillin in the treatment of human infection have been largely concerned with the maintenance of continuous levels of penicillin in the blood and tissues (22) This has been accomplished by the use of continuous intravenous drip, by frequent intramuscular injection, and by the development of the various types of repository penicillin products.

Recently, various clinicians have become interested in the possibility of applying the earlier information and have treated patients by means of penicillin injected at long intervals. These studies have considered principally the treatment of penumococcus pneumonia or hemolytic streptococcus respiratory infection on such schedules as one or two doses per day of 300,000 units of crystalline penicillin G dissolved in normal salt solution (23 to 26). In one study, Altemeier treated a large number of surgical infections on a schedule involving the administration of 100,000 units of penicillin in aqueous solution every eight hours (27) In general it may be stated that the results are comparable to those obtained with the more conventional methods.

Most of these studies have involved the treatment of disease caused by organisms highly sensitive to the action of penicillin There can be little doubt that a satisfactory regimen, suitable for the treatment of such infections, can be established involving the injection of soluble penicillin not more than twice daily. Loge & Kilbourne (28) indicated that single daily injection in the treatment of hemolytic streptococcus respiratory infection was not entirely satisfactory Organisms were not regularly eradicated from the nasopharyngeal tissues, the immunological response was not inhibited, nor was the development of rheumatic fever prevented. A recent clinical study by Jawetz (29) suggests that the administration of 150,000 units of penicillin in water twice daily is adequate insofar as bacteriological and clinical results are concerned. Jawetz did not measure antibody production nor follow patients *for development of poststreptococcal nonsuppurative complications.*

This information in regard to the efficacy of discontinuous penicillin therapy is primarily of academic interest. It is unlikely that widely spaced administration of penicillin in water will be used in the treatment of many infections in human beings caused by organisms highly sensitive to the action of penicillin since a satisfactory repository form of the drug is available. It would seem improper to recommend that such discontinuous therapy should ever be used in the treatment of disease in which the etiological agent

is moderately or highly resistant to the action of this antibacterial agent. Under these circumstances, it is desirable to use either large amounts of repository penicillin or to give the drug in the usual way by a series of relatively closely spaced intramuscular injections.

*Penicillin dosage.*—Eagel & Musselman (30) have recently explored the rate of the bactericidal action of penicillin *in vitro* as a function of its concentration. They demonstrated that there was a minimally inhibitory and a maximally effective concentration which was from two to twenty times greater than the former. A thirty-two thousand fold increase beyond this latter level did not further increase the effect of the drug. It was also observed that, when the amount of penicillin greatly exceeded the maximally effective concentration, many organisms were not as rapidly killed as they had been by smaller amounts of this agent. This observation had been made previously by Kirby (31), using *S. aureus* as a test organism.

The clinical implications of this study are not entirely clear. The maintenance of blood and tissue levels of penicillin greater than approximately 20 times the sensitivity as determined *in vitro* probably will be without advantages. Successful management of the vast majority of infections caused by organisms sensitive to the action of penicillin will therefore be accomplished by the administration of 300,000 to 600,000 units of penicillin per day. The paradoxical zone phenomenon mentioned above, in which high concentrations of penicillin kill organisms less well than do lower ones, may well not be of great significance. No evidence has as yet been presented which indicates that the over-treatment of bacterial infections with penicillin has been associated with inferior clinical results.

In summary, it is well to note that too much weight may have been attached in the past to the significance of penicillin blood levels. Disease may be treated successfully in the absence of well maintained concentrations of penicillin in the blood and tissues, and final answers have not yet been obtained in regard to the optimum dosage of penicillin for the treatment of various infections. Massive treatment with plasma concentrations greatly exceeding the optimal effective level probably offers no advantages. Nevertheless, a certain tendency to eliminate the measurement of blood levels of penicillin as a control on the efficacy of new penicillin products is to be deplored. It is difficult to know whether a new product is adequately absorbed unless quantitative measurements are made.

### Dihydrostreptomycin

Streptomycin continues to be the most effective therapeutic agent for use in the treatment of tuberculosis and is also valuable in many infections caused by gram-negative organisms, although here it will doubtless be soon replaced by other [illegible]

referred to the excellent review issue of the *American Journal of Medicine*

(32), and to the book, *The Therapeutic Value of Streptomycin*, by Keefer & Hewitt (33).

A distinct disadvantage to the use of streptomycin has been the high incidence of toxicity, particularly that involving the eighth nerve, leading to vestibular dysfunction and occasionally to deafness. Recently, the results of experimental study of a slight chemical modification of streptomycin, known as dihydrostreptomycin, have become available. This new compound has been shown to be much less toxic than streptomycin and usually may be given in doses of from 1 to 2 gm. a day for long periods of time without the development of vestibular difficulties. Eighth nerve damage has occurred, particularly when more than 2 gm per day have been administered. Patients receiving this drug must be carefully watched for signs of toxicity. Persons who have already exhibited reactions after the administration of streptomycin will often accept dihydrostreptomycin without difficulty (34 to 39).

From the standpoint of infectious disease, dihydrostreptomycin replaces streptomycin in every category. An organism which has become highly resistant to the latter will also be resistant to the former. There appears to be no role at the present time for the use of streptomycin except in a patient who has become sensitive to dihydrostreptomycin. In such a case it might be desirable, if further therapy were indicated, to undertake a trial with the older drug

## Aureomycin

Aureomycin, an important new antimicrobial agent discovered by Duggar, is produced by *Streptomyces aureofaciens* (40). Solutions in water are golden brown and highly acid It inhibits the growth of a wide variety of gram-negative and gram-positive organisms in low concentrations *in vitro* (41), and antiviral and antirickettsial effects have been demonstrated by the study of experimental psittacosis, lymphogranuloma venereum, spotted fever, and typhus (42, 43). Development of resistance to aureomycin by microorganisms has been accomplished *in vitro* with great difficulty. In this respect it resembles penicillin and differs sharply from the sulfonamides and streptomycin.

Aureomycin is unstable and deteriorates rapidly in solution in various solvents and in body fluids This characteristic of the drug has made pharmacological studies, including investigation of absorption and excretion, and the measurement of blood and tissue levels, difficult. Two studies (44, 45) were in essential agreement in that oral administration of an initial dose of 1 gm in adults was followed by the development of significant concentrations in the blood in 1 hr. and maximum concentrations within 2 to 4 hr. Large amounts of aureomycin appeared in the urine (46) but the agent was excreted much more slowly than penicillin since the levels in the serum were maintained for several hours. When the drug was administered on a continuous schedule, 1 gm. being given every 4 to 6 hr., the levels increased gradually. This was noted as early as the second dose, but usually was more

marked after several days. In some cases the later blood concentrations exceeded the earlier ones by many fold.

Administration of aureomycin by mouth has been practical and widely used but it is clear that absorption from the gastrointestinal tract must be poor since the intravenous injection of 100 mg. is associated with the attainment of serum levels comparable to those observed following the oral exhibition of 1 gm. (45). Intramuscular injection is impractical because of extreme local pain at the site of injection. The preparation of solutions suitable for intravenous injection of aureomycin has been difficult and thrombosis of the veins following the use of this route has been a frequent occurrence. It is probable that these technical difficulties will be resolved in part in the near future. It is a matter of some importance since, although aureomycin has proved to be notably nontoxic, nausea and vomiting have occurred frequently following its administration by mouth. Parenteral therapy will, therefore, be indicated in many instances.

The daily dose of aureomycin and the duration of therapy necessary for the treatment of various human infectious diseases have not yet been fully evaluated. Many investigators have used from 2 to 4 gm. daily.

Investigation of the value of aureomycin in several rickettsial diseases is now quite complete and it is obvious that this drug is remarkably effective in disorders caused by these infectious agents. The course of typhus and of Rocky Mountain spotted fever is profoundly altered (47 to 50). The temperature returns to normal in association with rapid clinical recovery within 24 to 48 hr after the administration of rather small amounts of aureomycin for 1 to 2 days. Good results have also been described in Q fever (51) but this rickettsial disease is somewhat more resistant to the action of aureomycin than are the others in that the course of the illness is terminated more slowly, treatment must be continued over a longer period of time, and occasional failures have occurred.

Two virus diseases, psittacosis and lymphogranuloma venereum, caused by related agents, have been stated to respond well to treatment with aureomycin (52, 53). Several reports have also appeared describing the use of aureomycin in the treatment of the disease known as primary atypical pneumonia which is presumably of viral origin (54, 55). These preliminary studies suggest that this agent has a striking effect on the course of this common disease. It should be noted that no well-controlled investigations have appeared, and at least one group of investigators has suggested that recovery in aureomycin-treated patients was no more prompt than in those who had not been treated with this drug (56). Nevertheless, it is probable that aureomycin will prove to be of value in the treatment of the severe forms of this type of pneumonitis.

Evaluation of the proper role of aureomycin in therapy of bacterial disease is quite incomplete. The drug has a considerable effect on the course of brucellosis, which will be described in another section of this review. It does not convincingly alter the natural history of salmonella infections such as

typhoid fever (57). The results in gonorrhea are not particularly impressive (58). Recovery from pneumococcus pneumonia has occurred following its administration but the number of reported cases is too small for any conclusions to be drawn as to its efficacy in comparison with penicillin (59). Woodward and his associates believe, on the basis of a very limited clinical experience, that aureomycin is comparable in effectiveness to streptomycin in the management of tularemia (60).

The most numerous clinical uses for aureomycin probably will be found in the treatment of urinary tract infections caused by both gram-positive and gram-negative organisms (61), and in the complications of intra-abdominal accidents associated with peritonitis. It should be borne in mind in regard to the former, that cure of the disease by antibacterial therapy cannot be expected in the presence of obstruction, distortion, or malformation of the urinary passages Under these circumstances, reinfection with organisms resistant to the action of the antibacterial substance will invariably occur.

### CHLOROMYCETIN

Burkholder and his co-workers at Yale University isolated a new antimicrobial agent, chloromycetin, from an actinomycete recovered from soil obtained in Venezuela (62). Bartz has determined its structure; it has been synthesized, and given the chemical name of chloramphenicol (63). Preliminary investigations indicate that the synthetic product is identical in its biological activity with that produced by the fungus (64). It may be measured in the blood and tissues by colorimetric methods (65).

Chloromycetin has not been prepared in form suitable for parenteral use It has been administered by mouth in doses from 2 to 4 gm. per day. Optimal dosage schedules have not yet been devised No toxic reactions of any kind have been reported (66).

The antibacterial spectrum of chloromycetin is broad and similar to that of aureomycin (67). Furthermore, studies of experimental disease have indicated that chloromycetin should be efficacious in the treatment of infection by the large viruses and by rickettsia (68, 69). Several clinical studies have indicated that this is indeed the case, typhus and Rocky Mountain spotted fever being controlled very promptly by its use (70 to 73) It is not yet known whether chloromycetin will be of value in the management of the large virus diseases and in primary atypical pneumonia. Its administration to human beings with typhoid fever has been followed by prompt and dramatic remissions but a considerable number of the patients treated have relapsed (74). Few have received a prolonged therapy and this may be necessary if the infection is to be eradicated.

Chloromycetin and aureomycin will apparently be of comparable value in the management of brucellosis (75). It will doubtless be of very great value in urinary tract infections caused by gram-negative organisms (76) and in gonorrhea (77)

### Polymyxin

An interesting antibiotic, named polymyxin by American workers (78), and aerosporin by English workers (79), has *in vitro* activity against a number of gram-negative organisms Preliminary investigation has revealed that the administration of this substance in animals and human beings is regularly associated with renal damage (80) which may be severe and irreversible. This toxic effect is believed to be inherent in the active principle. It is probable that this drug will be entirely unsuitable for use in clinical medicine.

### Bacitracin

A new antibiotic, produced by a member of the *Bacillus subtilis* group and called bacitracin, was described in 1945 by Meleney and co-workers (81). This material has since been prepared in sufficiently large amounts to permit clinical trial Its antibacterial spectrum is very similar to that of penicillin. An early report by Meleney & Johnson (82) indicated that the drug might well have value when applied locally to infected tissues. Other studies in rabbit syphilis (83), and in the treatment of surgical infections in human beings (84), demonstrate that bacitracin is definitely effective when administered parenterally. It must be injected since it is not adsorbed when given by mouth.

Unfortunately, the preparations presently available are profoundly nephrotoxic (85, 86) Meleney *et al* (84) have claimed that the renal damage is the result of impurities in the material supplied by a commercial firm and that the earlier materials made in his laboratory were nontoxic Its use by the parenteral route in human beings must obviously await the solution of these problems. If the agent cannot be prepared on a commercial basis in a nontoxic form, it may have considerable merit as a local chemotherapeutic agent. It is now available for this purpose in an ointment.

### Combined Antiobiotic Therapy

Combinations of antibacterial agents have been used empirically, for some time, particularly in the management of infection following intra-abdominal accidents The results obtained under these circumstances have been difficult to evaluate and it has been impossible to determine whether two or more of these drugs together were really more useful than any one separately. Spink and his associates (87) have reported the cure of *Brucella* endocarditis with a combination of sulfadiazine and streptomycin but, in this situation, it has been believed that the sulfonamide merely suppressed the development of resistant variants as they appeared This could not be regarded as a truly synergistic or even additive effect

The recent report of the treatment of enterococcal (*Streptococcus faecalis*) endocarditis with streptomycin and penicillin has been most instructive Several patients recovered who received 2 gm of the former and 5 million units of the latter per day (88). Neither drug alone, in these amounts, would

have been expected to have had any effect on the illness and all of the patients had, in fact, received larger amounts of penicillin without alteration of the course of the illness. True synergism was not demonstrated *in vitro* and the clinical results have not been fully explained.

These observations suggest the potential value of this type of therapy. Reports of investigations of the use of the five presently available antimicrobial drugs in various combinations and in various diseases will certainly appear in the future.

## Bacterial Resistance to Antimicrobial Agents

*Acquired resistance to the action of the sulfonamides by microorganisms* was frequently a limiting factor in the application of these agents in the treatment of infectious diseases. It soon became apparent that this phenomenon would be much less frequently observed when penicillin was used as the antibacterial agent. Nevertheless, numerous investigators have shown that microorganisms do develop an increased resistance to the effects of this drug and that this has been responsible for occasional clinical failure. Hirsh and his associates have described 14 cases in which increasing penicillin resistance occurred during treatment (89). All were bacteremic and endocarditis was present in nine. A staphylococcus was the etiological agent in ten. Careful bacteriological control indicated the need for larger amounts of penicillin or a change to streptomycin. Only two of the group died of uncontrolled infection

Demerec (90) has stated, and his ideas have received wide acceptance, that this development of resistance to penicillin is because of the appearance of resistant mutants, each of which is only slightly less well inhibited by the antimicrobial agent than was the parent strain. It is believed that each mutation leading to a further increase in resistance must occur serially. Since only a very few of these mutants are produced per generation of bacteria, it is clear that penicillin resistance will be developed only with considerable difficulty.

An entirely different situation has been shown to prevail when streptomycin is studied (91). Resistance to this agent also develops by step-wise mutation but, in addition, another mechanism is operative in which variants, enormously resistant to the action of streptomycin, are formed in any generation. This permits the very rapid development of streptomycin-resistant bacterial populations, either *in vitro* or *in vivo*. It is well known that clinical failure with streptomycin is a regular event unless the infectious process is [illegible]

(91) have discovered that a certain number of bacteria highly resistant to streptomycin will actually be dependent upon this chemical for growth. Animals inoculated with such strains become ill if streptomycin is administered and recover when it is withdrawn No clinical significance apparently need be attached to this observation at the present time.

Detailed information in regard to the development of resistance to the newer antimicrobial agents, aureomycin and chloromycetin, has not yet appeared in detail. Preliminary observations indicate that they will resemble in this respect penicillin more closely than either streptomycin or the sulfonamides, but it is known that bacteria will become resistant to both (92).

## Effect of Antibiotics upon the Normal Flora

It has been apparent for several years that the administration of antibacterial substances may have a profound effect upon the normal flora of the body cavities. These alterations are of two general types. In one, elements of the normal flora disappear and are not infrequently replaced by other microorganisms that are resistant to the action of the antibacterial agent. The administration of poorly absorbed sulfonamides by mouth creates such a situation in that coliform organisms will be greatly reduced in number in the feces, and enterococci become the predominant organisms (93).

More recently, the effect of penicillin on the aerobic flora of the normal throat has been explored (94, 95). Since the cultural methods used by the different investigators have varied, their results may not be compared in detail. In general, it may be stated that early in the course of the administration of penicillin the usual, essentially gram-positive flora of the throat is replaced by gram-negative organisms of the *Hemophilus* and *Neisseria* groups. With continued administration of the drug, gram-positive cocci are likely to reappear. Similar changes are frequently observed during the course of treatment of individuals with pulmonary infections. It is not uncommon to observe the complete disappearance of the original streptococci and the emergence of a flora in the sputum in such individuals in which all of the organisms are either gram-negative or highly penicillin-resistant gram-positive cocci. One frequently observes sputum from which pure growths of coliform organisms are obtained. Such findings were unprecedented before the advent of penicillin.

Another type of change which may occur in the normal flora is the development of a high degree of resistance to the antibacterial agent by organisms which are already present in the area. This occurs regularly when streptomycin is given either by mouth or parenterally. With either of these modes of administration, variants of the coliform bacilli, highly resistant to streptomycin, rapidly appear in the feces, and disappear again within 30 days after the drug has been withdrawn (96, 97). Similarly, the flora of the nasopharynx rapidly becomes resistant to streptomycin when this agent is given parenterally (98).

Related changes also occur in regard to staphylococci and penicillin. Barber & Colleague (99) showed that penicillin-resistant staphylococci were isolated from a high percentage of patients in whom a hospital infection with these organisms had supervened. Large numbers of hospital personnel carried such resistant strains in the nasopharynx. It was suggested that such alterations in the flora were the result of contact of these individuals with patients who had received penicillin and who had developed resistant staphylococci

in their respiratory flora. More detailed studies, that will demonstrate the frequency of occurrence of penicillin-resistant staphylococci in persons who have received penicillin and in infectious disease in general, are indicated

The clinical implications of these changes in bacterial flora as the result of the administration of antibacterial agents have not yet been thoroughly evaluated. It is evident that a balance exists between the various members of the normal flora and that this relationship cannot be disrupted without the appearance of large numbers of organisms of types not usually predominant in the particular area For the most part the new bacteria that emerge under these circumstances are of low invasiveness and their presence has not been cause for alarm.

Examples of superinfection have, however, been described by a number of investigators Weinstein's report (100) is of the greatest interest. He has observed staphylococcal sepsis with bacteremia on two occasions during the course of treatment with streptomycin of influenza bacillus meningitis in infants. Another child, receiving penicillin for the treatment of a pneumonia of unknown etiology, developed Type B influenza bacillus bacteremia. Similar generalized infections by *Pseudomonas aeruginosa* during the course of penicillin therapy have been reported by Stanley (101). Pulmonary superinfections with members of the coliform and Friedlander's group of gram-negative bacilli have also occurred (102). Only a few of these complex multiple infections have been reported but these situations may well arise more frequently than is realized Careful bacteriological examination of the blood, sputum, urine, and other indicated materials should invariably be carried out during antibiotic therapy in any patient who does not recover promptly.

A somewhat different problem is presented by the previously mentioned appearance of staphylococci, highly resistant to the antibacterial action of penicillin. It is now evident that such organisms will be isolated very frequently, not only from suppurative lesions that have failed to heal promptly during the administration of penicillin, but also from new illnesses in persons who have previously received this antibiotic, and in persons who develop staphylococcal disease in hosptials There is not any convincing evidence as yet that the "wild" staphylococci in the population at large have become more than occasionally insensitive to penicillin. Staphylococcus infection, occurring in persons in the categories above, is, however, so likely to be caused by resistant organisms that in such cases *in vitro* penicillin sensitivity tests of isolated staphylococci should invariably be made The use of another antistaphylococcal agent, such as aureomycin or streptomycin, will frequently be indicated in such cases

## BACTERIAL DISEASES

Little new information in the field of bacterial disease in man has been forthcoming recently that is of general interest. Only infections caused by hemolytic streptococci and the brucella will be considered in detail in this review.

### Hemolytic Streptococcus Infection

Intensive investigation of hemolytic streptococcus disease during the last decade has materially advanced the understanding of these disorders. The work that has been done may be summarized in four categories.

*Bacteriology*.—It is now known that the hemolytic streptococci responsible for nearly all primary infections, particularly of the respiratory passages in human beings, are caused by organisms of a single serological group designated by the letter "A." The members of this group may be further subdivided into types by serological methods. Epidemiological application of these techniques has revealed that one small group of types is responsible for the bulk of streptococcal disease in any community in any season. A unitarian point of view in regard to hemolytic streptococcus infection has evolved as the result of these observations It is clear that the clinical nature of disease caused by these organisms is the result of a concatenation of factors involving the invasiveness and virulence of the infectious agent, the antitoxic and antibacterial immunity of the host, and the portal of entry of the organism into the tissues. No specific streptococcus of scarlet fever, erysipelas, or other disease exists.

Important information obtained during the study of epidemics of streptococcal respiratory disease in military personnel revealed, however, that strains of Group A hemolytic streptococci may differ from one another in regard to important biological properties. Several types were unable to induce rash formation (scarlet fever) over a period of more than two years (103), even in individuals known to be Dick positive (104) Other studies demonstrated that certain strains failed to elaborate streptokinase (fibrinolysin) *in vitro* and to stimulate vigorous antistreptokinase (antifibrinolysin) production in infected persons (104, 105). It was also shown that the magnitude of the antistreptolysin response was greater following infection by certain strains (104). Other investigators have observed that differences exist between the ability of certain strains to make hyaluronic acid and the enzyme hyaluronidase *in vitro* (106)

It is not known whether these variations in the capacity of various streptococci to form potentially important active substances are fixed characteristics of the strain or whether they may be altered from season to season, and host to host The military experience suggests that they are relatively permanent.

The final importance of the demonstration of such biological differences between the streptococci of Group A has not been determined This information does not materially alter the unitarian point of view of hemolytic streptococcus infection mentioned above, yet it is obvious that if these organisms are often unlike one another in regard to these measurable substances, they may be very dissimilar in regard to other attributes as well It is probable that, if these studies and others of this type are ever of value in elucidating any of the aspects of streptococcal disease in man, it will be in relationship to the pathogenesis of the late, nonsuppurative post-

streptococcal complications. No correlation of these biological differences with any aspect of the acute suppurative process has yet been possible with the exception of those which relate to the production of skin rash.

Additional important investigations, which will not be reviewed here, have centered around the streptococcal cell and its products. The interested reader is referred to the excellent review by Rammelkamp & Dingle in volume II of the *Annual Review of Microbiology* (107).

*Acute suppurative phase.*—The concept of the nature of the acute suppurative phase of hemolytic streptococcal infection of the respiratory tract has been altered in recent years as the result of the studies of Powers & Boisvert at Yale (108, 109). These investigators have stated that hemolytic streptococcal respiratory infection may be divided into three phases The first of these, that of infancy and early childhood, is characterized by insidious onset mild rhinopharyngitis, low grade persistent fever, cervical adenitis, catarrhal or suppurative otitis media, anemia, and a prolonged clinical course which may be promptly terminated by the administration of antibacterial agents such as penicillin. Suppurative complications are common events; nonsuppurative complications are exceedingly rare.

In middle childhood, the nature of the disease process alters in that the onset may become more abrupt, the course shorter but more acute and severe, and the physical signs change, so that exudative tonsillitis may become a prominent feature A skin rash (scarlet fever) is commonly seen in these children Suppurative complications, such as otitis media and cervical adenitis, often occur. More important is the appearance in this group of the nonsuppurative disorders, such as rheumatic fever.

In older children, and in adults, hemolytic streptococcal respiratory infection is much like that seen in middle childhood except for the disappearance of the skin rash (scarlet fever) as a common manifestation of the disease process. Suppurative complications in this age group are uncommon but nonsuppurative disorders occur frequently.

The diagnosis of the mid-childhood and adult types of hemolytic streptococcal respiratory infection is often possible on the basis of history and physical examination alone This is not the case with the infantile type of this disease. No distinguishing clinical feature in the absence of suppurative complications of the ears or neck glands have been described which permit its accurate differentiation from the common nonbacterial respiratory infections Cultural examinations of material obtained from the nose and throat are essential if one is to establish accurate diagnoses of streptococcal disease in young children. Such diagnosis has become increasingly important with the advent of potent antibacterial agents such as penicillin, since it is clear that prolonged debilitating illness in infants and young children may often be dramatically terminated by the exhibition of these agents if the disease is streptococcal in origin, but such therapy is of no avail if the disease is caused by a filterable virus

Boisvert & Walcher (110) have recently described the frequent occur-

rence of hemolytic streptococcus vaginitis in children. The etiology of this disease is ordinarily unrecognized and its importance has not been appreciated. The value of complete cultural examination of materials obtained from the vagina in instances of vaginitis in childhood cannot be overemphasized.

*Relationship of hemolytic streptococcal infection to rheumatic fever.*—During the past 20 years it has become increasingly apparent that infection by hemolytic streptococci is in some way related to the development of the rheumatic state. The evidence on which this fact has been based has been of an indirect nature and may be summarized as follows: (*a*) Rheumatic fever has been a sequel to known hemolytic streptococcus infections, particularly of the respiratory tract; (*b*) epidemics of rheumatic fever often follow outbreaks of scarlet fever or streptococcus sore throat; (*c*) recrudescences of activity frequently appear when infection by hemolytic streptococci occurs in persons who have previously undergone attacks of rheumatic fever; (*d*) immunological investigations have demonstrated that high titers of various antistreptococcal antibodies and cutaneous hypersensitivity to products and fractions of hemolytic streptococci are usually demonstrable in persons suffering from acute rheumatic fever or from recurrences of this disease.

Additional information obtained during the study of epidemics of hemolytic streptococcus infection in the armed forces during the recent war demonstrated that rheumatic fever did indeed occur only following infection by Group A hemolytic streptococci (111). These studies described in detail the sequence of events following infection by the hemolytic streptococcus and pointed out the great frequency and complex nature of the nonsuppurative disorders which are such common sequels The most important of these are the syndromes of the rheumatic state in which fever, arthritis and carditis occur in various combinations (112, 113)

The intimate association between hemolytic streptococcal infection and the rheumatic state has been established by the investigations described above but details as to fundamental mechanisms involved have been lacking. Evidence was presented by Rantz, Boisvert & Spink (111) which indicated that serial reinfection by different serological types of Group A hemolytic streptococci might be essential if rheumatic fever were to occur. Murphy & Swift, in a brilliant study (114), used multiple, serial, dermal infection of the rabbit by strains of this organism of different types as an experimental tool. Five to ten infections over a period of a year or more were often followed by sickening of the animal and the development of a new disease not associated with dissemination of organisms from the local lesion. Anatomical study of the tissues of these animals revealed lesions indistinguishable from those seen in fatal rheumatic fever in human beings The reviewer believes that the experimental production of rheumatic fever in a laboratory animal may be regarded as accomplished and the essential role of reinfection by Group A hemolytic streptococci in its causation as established.

The mechanisms by which such infections produce the nonsuppurative poststreptococcal disorders have not been elucidated. The suggestion was

made early in the century that some type of altered immunological reaction of an allergic nature might be responsible The recent reemphasis by Rich & Gregory (115) of the widespread occurrence of tissue and vascular lesions during the height of the allergic reaction in human beings sensitized with sulfonamides or horse serum, and in experimental animals similarly sensitized with horse serum, has reawakened great interest in the possible allergic nature of the poststreptococcal disorders. It is now clear that an immunological reaction, presumably the result of the interaction of an antigen and an antibody in the host tissues, will often result in the production of lesions that are in some respects like those seen in rheumatic fever. It is very difficult to go beyond this simple observation and to attempt to define fully the experimental or human disease. Consequently, many investigators have turned to a study of circulating antibodies in the hope that the presence of one in excessively great concentrations in the serum of rheumatic individuals might provide a clue to the nature of the process and to the identity of the possible sensitizing antigen of the hemolytic streptococcus responsible for the development of the rheumatic state.

The substances studied were antistreptolysin "O" (116, 117, 118), antistreptokinase (118, 119), antibacterial precipitating antibodies (120), type-specific bacteriostatic antibodies (121), complement-fixing streptococcal nucleoproteins (122), and gamma globulin (118). These investigations demonstrated that the individual infected by Group A hemolytic streptococci who was to develop a poststreptococcal nonsuppurative complication formed, on the average, a larger amount of these substances in his serum than did the individual who did not develop such a complication. Only agglutinins for autoclaved Group A hemolytic streptococci have not followed this pattern (123) There was no evidence that any one of these substances was directly related to the pathogenesis of the rheumatic state. It was of interest to learn that individuals who developed a disorder, possibly of an immunological nature, had exaggerated immunological responses This evidence enhances the position of the allergic hypothesis in the pathogenesis of the rheumatic state.

More recently another substance, antihyaluronidase, an antibody which is capable of neutralizing the streptococcal enzyme that splits hyaluronic acid, *has been studied in the serum of human beings The earlier* investigations of Friou & Wenner (124), and of Quinn (125, 126) demonstrated increased concentrations of this immune substance in the serum of rheumatic individuals. They failed to show conclusively that it was present in such persons in amounts greater than one might have expected by analogy with previous immunological observations just described

Harris & Harris (127) have studied this same antibody and have demonstrated that the amount present in the serum of rheumatic individuals with carditis is very great indeed. Excessively high levels are not found in polyarthritic rheumatic fever without cardiac involvement (128). These observations have centered current interest about the hyaluronic acid-hyaluronidase

system. Its role in the pathogenesis of the important poststreptococcal nonsuppurative diseases cannot now be determined

Wilson is perhaps the only prominent current investigator who has failed to satisfy herself that there is an intimate relationship between infection by hemolytic streptococci and the development of rheumatic fever. Several of her co-workers studied streptococcal agglutinins (129) and complement titers (130, 131) in normal and abnormal conditions and have failed to discover any increase in the amount of agglutinating antibody or any decrease in the amount of complement during the course of rheumatic fever.

These workers also present a very extensive study of the concentration of gamma globulin as determined by electrophoretic analysis in the serum of the rheumatic subject (132, 133). They note that there is a more intimate relationship between the presence or absence of a preceding respiratory infection (before the onset of the rheumatic fever) and the concentration of gamma globulin than there is between the presence or absence of evidence of rheumatic activity. This is in contrast to the previously mentioned observations of Anderson, Kunkel & McCarty (118) who, using a different method discovered large amounts of gamma globulin in the serum of the rheumatic individual. These discrepancies may be the result of differences in experimental techniques since the floccuation method of Kunkel may well not measure the same plasma protein as does the electrophoretic determination of gamma globulin.

*Antibacterial agents in hemolytic streptococcal disease.*—Although sulfonamides have a striking effect on the mortality rate in hemolytic streptococcal sepsis and meningitis, it has not been possible to show that their administration greatly alters the course of the adult type of hemolytic streptococcal respiratory infection. It is also known that their use does not affect the production of antistreptococcal antibodies during convalescence nor the incidence of late nonsuppurative complications (136). Similarly, when penicillin is administered in adequate amounts, it is difficult to show that the acute respiratory illness has been materially affected (134). If this agent is administered for too short a time (3 days or less), bacteriological and clinical relapse are frequent events. It should be noted that penicillin has a profound effect on the infantile type of hemolytic streptococcus respiratory disease and that its use may be associated in all age groups with a reduction in the incidence of suppurative complications, such as otitis media and cervical adenitis.

A number of different studies have now demonstrated that, if penicillin is given early in adequate [illegible]

from the nasopharyngeal tissues in most instances (135) More important is the observation, now repeatedly confirmed, that the production of antistreptococcal antibodies is quantitatively greatly impaired (118, 136, 137, 138).

There is also information which suggests that the type of adequate peni-

cillin therapy just described may also interfere with the development of late poststreptococcal complications such as rheumatic fever (113, 135, 138). These observations, if they are confirmed in larger groups of patients, are of potentially great importance and indicate that it may be possible to prevent the development of rheumatic fever by the proper management of the initial acute suppurative illness.[3] While such treatment is not feasible or indicated for all examples of streptococcus respiratory disease in the population at large, it is particularly applicable to those persons known to be highly susceptible to the development of the rheumatic state. Proper management of the rheumatic subject may include in the future frequent culture of the nasopharynx, particularly during episodes of respiratory disease, and the vigorous treatment with penicillin of those proven to be caused by the hemolytic streptococcus. It may be thus possible to reduce materially the incidence of recrudescences of rheumatic fever in such individuals.

## Brucellosis

Brucellosis has been repeatedly stated to be a common disease in human beings in the United States That this should be so is not surprising since it is known that large numbers of domestic animals, particularly cattle and hogs, are frequently infected by *Brucella*. Transmission of this disease to human beings through unpasteurized milk and the handling of infected animal materials may readily occur. In spite of these facts, it is curious that virtually no comprehensive studies of the clinical disease in man have been carried out since the investigations of the Mediterranean Fever Commission in 1907. As a result of this lack of study of the natural history of this important disease, many misconceptions in regard to its nature in man have arisen. It is encouraging, therefore, that interest in these problems has increased in recent years and that at least one well supported group of investigators is carrying out an intensive laboratory and clinical study at the University of Minnesota under the direction of Dr. Wesley W. Spink. A few publications from this group have already appeared, most of which bear upon the tissue reactions to *Brucella* as studied in the experimental animal and in the embryonated hen's egg, and to experimental and clinical use of various antibacterial agents in the treatment of this disease (140, 141, 142). It is hoped that a comprehensive description of the entire clinical picture of the diesase will shortly be published by these workers

In one important paper (143), Spink notes that the liver is involved frequently in acute brucellosis and states that he believes that this infection may be a contributing cause of serious chronic disease of this organ. The occurrence of osteomyelitis, spondylitis and endocarditis as complications

of brucellosis are emphasized. He also makes the interesting observation that reinfection with *Brucella* may occur.

In another paper which will not be seen by many physicians, since it was prepared for the Veterans' Administration, Spink makes certain statements about brucellosis which are of such great importance that they will be quoted extensively below (144). In regard to the natural history of the disease, he makes the following comments:

Reading the modern literature on brucellosis, one gains the impression that active brucellosis is primarily a chronic disease. But the carefully analyzed records of hundreds of cases in Malta made by Eyre almost 50 years ago resulted in the following statement: "One may safely say that not more than 10 per cent are convalescent in a shorter period than one month from the onset of symptoms. In 50 per cent, the disease extends over two months, in 25 per cent to three months, and in fully 15 per cent, a duration of three months is exceeded." It is to be recalled that Eyre was concerned with cases caused by the most invasive species, *Br. melitensis*, and that no specific therapy was available at that time. Investigations carried on at the University of Minnesota hospitals over a period of 10 years with cases due mostly to *Br. abortus* corroborate the findings of earlier observers in melitensis infections. There is no doubt that bacteriologically proven cases of abortus brucellosis may be persistently ill for months or years, but culturally proved disease persisting for over a year is exceptional.

Chronic brucellosis has been described as a vague illness characterized by weakness, generalized aches and pains, anorexia, constipation, nervousness, and without abnormal physical findings If only a minority of the culturally proved cases of brucellosis persist with evidence of active disease longer than three months, why is the diagnosis of chronic brucellosis made so frequently today; and why has such a vigorous, but unconvincing, defense been made in the literature of the diagnostic criteria attending it? There are several reasons why the diagnosis is made so frequently In the first place, the symptoms ascribed to chronic brucellosis are those associated with such functional illness as psychoneuroses and anxiety states. Hundreds of these functionally disordered patients haunt the offices of physicians every day Oftentimes in desperation, and only too often as a result of unbridled enthusiasm, the physician attempts to explain functional complaints upon an organic basis and chronic brucellosis solves his diagnostic dilemma He reassures himself and the patient that brucellosis is the cause of the illness by eliciting a positive intradermal reaction with *Brucella* antigen. It cannot be denied that once in a while a patient with undoubted brucellosis has been labelled as a psychoneurotic, but this mistake occurs less often than does the reverse Another explanation for the frequency with which the diagnosis is made today is that patients may be suffering from the residuals of brucel- [illegible]

[illegible]

A belated diagnosis of brucellosis may be entertained, particularly if there is a history of possible exposure, if the intradermal test is positive, and if agglutinins are present

in the blood Unfortunately, instead of the patient receiving the reassurance that he has passed the active form of the disease and is struggling through the difficult period of convalescence, he is often subjected to a time-consuming, expensive, and frequently fruitless "desensitization" or "immunization" program with *Brucella* antigen, or is treated with potentially dangerous chemotherapeutic agents. It can only be concluded that while chronic brucellosis does occur, the diagnosis is all too frequently based upon inadequate data

Later, he discusses diagnostic procedure and emphasizes the necessity for the isolation of *Brucella* from body fluids and tissues, particularly the blood, if a precise diagnosis is to be made. He condemns the use of the opsonocytophagic index and the intradermal tests with *Brucella* antigen. Reliance should be placed upon the agglutination test and on blood cultures and, if both of these procedures yield negative results, there is little to be gained by eliciting a positive skin test. He then comments upon the agglutination reaction as follows:

A simple and dependable method for screening active cases of brucellosis is the agglutination test. Agglutinins may be detected by either a rapid slide test or by diluting serum in a series of tubes and noting, macroscopically, the clumping of organisms after a suitable period of incubation. The latter procedure usually yields the more accurate information of the two. Success with the agglutination test is dependent in great part upon the use of a proper antigen. A suitable antigen is supplied by the Bureau of Animal Industry of the Department of Agriculture. In performing the agglutination test, it is necessary to dilute the serum far enough to avoid the prozone phenomenon In an occasional instance, a serum may reveal no agglutinins in dilutions up to 1 to 160 or 1 to 320, while definite clumping may be seen in the higher dilutions. Less often, blocking antibodies (145) may be present so that a test performed according to the usual procedures may reveal no agglutinins It is frequently stated that in acute, and especially in chronic, brucellosis the agglutination test may often be negative But when the literature on this subject is reviewed critically, and the experience of several dependable laboratories is taken into consideration, this is found to be an unusual occurrence in bacteriologically proved cases Whenever agglutinins have been absent, the diagnosis of brucellosis has been suspect. Agglutinins may be absent in the first week or two of acute brucellosis. They may disappear from the blood upon recovery from the disease On the other hand, complete recovery may be followed by a period of years during which a relatively high titer of agglutinins may persist Although agglutinins may be absent following

> There is no titer of agglutinins that is specific for active disease. In general, the higher the titer, the more likely it is that one will isolate *Brucella* from the blood.
>
> One may summarize the value of the agglutination test as a diagnostic procedure by stating that it is a dependable laboratory aid if its limitations are kept in mind Except in the very acute cases, the test is positive in the vast majority of acute and chronic cases of brucellosis which are bacteriologically proved. But a positive test does not always represent active disease, and non-specific agglutinins for *Brucella* may occur.

This information indicates that the agglutination test is the most useful procedure in the diagnosis of brucellosis. It is well to bear in mind, however, that the techniques for performing this test are not well standardized. In a useful paper Eisele, McCullough & Beal (146) report the results of the multiple testing of several sera by different commercial laboratories In various hands, the same serum was either negative or strongly positive. It is essential, therefore, that the agglutination test be carefully performed by competent laboratories if satisfactory evaluation of the results is to be made.

The most important developments in the management of brucellosis during the past year have been the reports of cure of this disease by the administration of various antibacterial agents. Previous studies have indicated that neither streptomycin alone, nor sulfonamides alone are particularly effective. Within the last year, Pulaski & Amspacher (147), Eisele & McCullough (148), and Spink, Hall, Shaffer & Braude (149), have described the treatment of this disorder with combined streptomycin and sulfadiazine. A suitable regime consisted of the administration of 2 gm. of dihydrostreptomycin per day for 14 days and 6 gm. of sulfadiazine per day for 21 days. Such therapy favorably altered the course of the infection in a high percentage of cases but relapse was discouragingly frequent Permanent eradication of brucella endocarditis has been accomplished (87)

More recently, Spink, Braude, Castaneda & Goytia have described the treatment of a number of cases of infection by *Brucella melitensis* with aureomycin (150) Similar studies by Knight, McDermott & Ruiz-Sanchez (50, 151), and by Woodward (75) have involved the use of this agent and also chloromycetin. The immediate effect of both agents on the acute illness has been dramatic. The temperature has promptly returned to normal, in association with great improvement in the sense of well-being of the patient, and the blood has been sterilized No advantage of one antimicrobial agent over the other has been demonstrated.

Relapse has already occurred in a considerable number of patients, many of whom have been [illegible]

that the original schedules be extended to [illegible] to 6 weeks of continuous therapy.

Whether these regimes will be followed by permanent arrest of the infectious process remains to be seen Previous experience with the chemotherapy of brucellosis suggests that they may not The availability of these agents should prove, in any case, to be a tremendous boon to the patient

suffering from the acute form of this disease. A prolonged and exhausting illness may be quickly terminated. If relapse occurs, a prompt response may again be expected It is possible that treatment of this infection may resemble that of vivax malaria in which each recurrence is terminated chemotherapeutically until that time when the immune mechanisms of the infected human are able to control the disorder.

Information as to the value of these agents in true chronic brucellosis is not yet available. It is possible that, if living brucella remain in the tissues, the results will be good If the syndrome presented by the patient is the result of neurotic complications of brucellosis, or of neurosis without brucellosis, the results of course will not be satisfactory.

Patients with acute and chronic brucellosis have been treated in the past with various antigenic preparations of brucella. The reports of the use of these agents have been uncritical and it is not clear whether they often have been of value With two different antibacterial agents capable of suppressing or eradicating brucella from the tissues available, it seems proper to recommend that such antigenic therapy be abandoned or used only very rarely.

## Miscellaneous Bacterial Diseases

Interesting new information which deserves comment has accumulated during the last two or three years in regard to a few bacterial diseases An important series of observations were those initiated by Goodpasture and his associates that established the bacterial etiology of granuloma inguinale (152). These investigators isolated a gram-negative bipolar bacillus in the chick embryo from the lesions of this disease. Subsequently, Dunham & Rake grew the organism on yolk, beef heart infusion agar slants and prepared antigens for serological testing (153). A recent report by Dulaney and associates describes techniques for the preparation of a stable and highly specific antigen for the complement fixation test (143). This procedure should be of value in diagnosis since the sera of nearly all infected persons gave positive tests, whereas healthy controls did not. Positive reactions were obtained with the serum of a number of individuals with early syphilis. Marshak & Rodriquez have demonstrated a striking response in the treatment of granuloma inguinale with streptomycin (155). Lesions which had been present for many months before treatment was instituted were healed after a period of two to three weeks. Several patients relapsed but the majority remained well. The Donovan bodies disappeared promptly after treatment was begun.

scopic, filterable form, and grow only in heavily enriched culture media in tiny colonies Stained smears of cultures reveal highly pelomorphic cells that divide by methods different from ordinary binary fission. Recently, Dienes, Ropes and their associates have reviewed their extensive experience

with this group of organisms as a cause of disease in human beings (156). These investigators have isolated "L" forms from the genitourinary tract of a large number of women. In only a few cases was it possible to discover any association between the presence of these bacteria and the disease process in the individual under study. A very different situation existed in males. Pleuropneumonia-like organisms were recovered from the genitourinary tracts of 58 male patients In nearly all there was evidence of prostatitis or cystitis, often of a very chronic sort. Even more impressive is the fact that arthritis was present in 27 cases, and in nine there was the classical syndrome of Reiter with arthritis, conjunctivitis and urethritis. In two cases, the organism was isolated from the joint fluid. In certain individuals the administration of streptomycin was associated with a prompt elimination of the infectious agent from the urinary tract with relief of symptoms. This occurred most dramatically in those patients with evidence of cystitis without arthritis. The effect on the course of the arthritic disorder was much less satisfactory.

These observations indicate that organisms of the pleuropneumonia group may be an important cause of genitourinary and arthritic disease, particularly in males. Additional information must be obtained before their importance can be fully assessed. Cultures suitable for the isolation of these microorganisms should certainly be obtained in all individuals in whom these various syndromes have been observed. It would be of particular interest to carry out such investigations in that group of disorders that have long been known to urologists as "abacterial pyurias."

Keogh & North (157) have demonstrated that *Hemophilus pertussis* forms a hemagglutinin which will cause clumping of the erythrocytes of various animal species. The agglutination is specifically inhibited by antibody. Preliminary investigation indicates that the hemagglutinin is intimately associated with the invasiveness of the microorganism and that the immune substance which reacts with it is responsible for protection of the experimental animal. These observations are of a preliminary nature but strongly suggest that their full exploitation may lead to a better understanding of infection by these bacteria and may well lead to more effective prophylaxis of whooping cough.

Other Australian investigators in a series of papers have described "a new mycobacterial disease" (158). It was first noted as a chronic cutaneous infection in a number of patients from a circumscribed area in that country. Histologically the lesions resembled leprosy and contained acid-fast bacilli which did not grow when the usual cultural techniques were applied nor did they cause disease in the usual experimental animals. A tentative diagnosis of leprosy was therefore made in these patients Later it was discovered that the organism would grow well at temperatures considerably lower than those which support optimal growth of the tubercle bacillus and other mycobacteria, and that it would produce lesions in the rat and in the mouse. It is not yet known whether this microorganism will be recovered from human

disease elsewhere in the world or whether it is capable of inducing an infectious process in organs other than the skin. It clearly must be borne in mind in the differential diagnosis of leprosy and must be considered when acid-fast bacteria are seen in lesions but are not recoverable by the standard cultural and animal techniques suitable for the isolation of tubercle bacilli.

## VIRUS AND RICKETTSIAL DISEASE

Clinically interesting developments in the field of virus disease during the last 18 months were relatively few. The discovery of new antibiotics, effective in the management of certain infections caused by viruses, as described above, were important These, and other earlier studies (159, 160, 161) demonstrate that the group of so-called "large" viruses, including those responsible for psittacosis and other disorders in birds, lymphogranuloma venereum, trachoma, inclusion blennorrhea, and mouse pneumonitis are susceptible to the antiviral action of a number of drugs including the sulfonamides, penicillin, streptomycin, aureomycin, and chloromycetin.

The smaller filterable agents have proved to be remarkably resistant to the action of any of these chemotherapeutic agents The subject of chemotherapy of infections caused by these viruses has been reviewed by Cutting *et al* (162, 163), who undertook an extensive investigation using the agents of Herpes simplex, vaccinia, and influenza A. This worker and his associates have screened an enormous number of chemicals of all sorts, searching for those which would give evidence of antiviral activity. None of the substances tried proved to be particularly efficacious, although a few, which were considered to be synthetic modifications of nulceic acid derivatives, slightly changed the course of infection by vaccinia virus in the chick embryo This infectious agent is similar in size to the other "large" viruses and might be expected to be more readily affected by external agents than the smaller viruses. This comment is of importance in the light of two reports, one describing the inhibition of canary pox virus by impurities in commercial penicillin (164), and a second reporting a similar result with an analogue of phenylalanine and vaccinia virus (165) The author is unaware of any convincing evidence that the natural history of experimental infection by the truly small agents has yet been altered chemotherapeutically.

Recent stimulating investigations have indicated that infection by the viruses of influenza A (166), mumps (167), and mouse pneumonitis (168), may be prevented by the presence of certain complex polysaccharides. It has been postulated that a virus must attach to a specific receptor on the surface of the cell before invasion The suggestion has been made that the molecule of polysaccharide may occupy this locus and prevent the fixation of the virus If this point of view be correct, it is likely that the mode of action of these substances may be regarded as prophylactic rather than therapeutic. There would seem to be no reason to suppose that the presence of polysaccharides could modify the course of disease after the virus has gained entrance to the cell.

Much of the work just described has been the result of study of red cell agglutination by various viruses. This will doubtless continue to be a valuable investigative tool, since living cell membranes of the susceptible host in the form of erythrocytes are freely available. This whole subject has been well and simply reviewed by Jawetz (169).

The respiratory viruses have continued to attract attention during the last two years. Immunization against influenza has been the subject of a number of communications. Two recent ones again describe the failure of this technique in the epidemic of influenza which occurred during the winter of 1946 to 1947 (170, 171). It is now known that this outbreak was caused by a virus similar to those previously associated with influenza A but differing sufficiently in its antigenic structure so that immunization with the older viruses was ineffective. This whole subject has recently been reviewed by Blake (172), who points out that protection against infection by the viruses of influenza was definitely conferred by subcutaneous immunization with formalin-killed virus in a number of carefully controlled earlier studies. He also notes the toxicity of the vaccine but refers to the recent investigation of Salk (173) which demonstrates that the antibody response does not increase proportionately with the concentration of virus and with the incidence of toxic reactions. It is possible that the administration of subtoxic amounts of the vaccine may be associated with an adequate enhancement of resistance to infection. This matter, and the use of the intradermal route of administration of the immunizing agent, will require not only additional immunological investigation but also clinical trial in the field before the results can be interpreted adequately. The unsatisfactory results obtained in 1946–47 are discussed. The United States Army has discontinued immunization after three years of trial since evidence that it was efficacious in reduction of the frequency of respiratory disease in troops was not forthcoming (174).

In planning a program of immunization against these important respiratory infections, it is absolutely essential that much greater additional information be obtained in regard to strain variations before widespread use can be recommended. It will be most desirable to have available the results of the rapid isolation and classification of viruses obtained from future outbreaks. If an infectious agent is antigenically different from the strains of virus included in the commercial stock vaccines then available, it is probable that it will be impossible to produce new vaccines containing the new and proper strain with sufficient celerity to permit their use during that epidemic. If the correct strain is not so included, then the use of the vaccine would be of no value. Elaborate programs for the isolation and classification of influenza viruses have been established by a number of agencies. Additional information and more complete recommendations as to the use of influenza vaccines should be forthcoming within a year or two.

*Isolation of respiratory viruses.*—It will be recalled that until recently only the viruses of influenza and of psittacosis and the related ornithosis

group had been isolated and proved to cause respiratory disease in human beings. During the war, the Commission on Acute Respiratory Diseases successfully transmitted a form of primary atypical pneumonia to volunteers by the use of filtered throat washings and sputum (175). More recently this group has described experiments in which nonpneumonic respiratory disease was also transferred to human beings in a similar type of experiment (176) Two agents, apparently immunologically distinct, caused disease in volunteers. One was isolated from a disorder which was characterized as the common cold; the other from a disease described as "undifferentiated respiratory illness." Homologous but not heterogenous immunity was conferred by infection with the latter virus. No immunity to the former was demonstrated The disease which was produced experimentally did not always resemble closely that observed in the original host.

Topping & Atlas (177) have reported the transfer of an agent, isolated and cultivated serially in the embryonated hen's egg, which produced an illness in volunteers The process from which the virus was originally obtained was a coryzal disorder of the upper respiratory tract (common cold). The experimental infection was similar. It is obvious that the use of volunteers is cumbersome. Progress in this field of investigation will be discouragingly slow unless some experimental animal or immunological techniques for the detection of the infectious agents can be discovered

Dingle (178) has recently summarized the clinical implications of the studies that have just been described and others. He believes that the viral respiratory infections, other than ornithosis and influenza, can be divided into four general categories that are clinically and epidemiologically distinct and that may be caused by different agents His grouping includes "the common cold," "nonbacterial exudative tonsillitis and pharyngitis," "undifferentiated respiratory disease," and "primary atypical pneumonia." The reviewer is in full accord with this classification and feels that most cases of respiratory disease can be fitted into this scheme if proper bacteriological examinations are made for the purpose of excluding hemolytic streptococcal sore throat and bacterial pneumonia

Relatively little new information in regard to the etiology, pathogenesis, and natural history of viral hepatitis has appeared within the last two years. Two important papers, however, should be discussed In one, Stokes and his associates (179) describe the efficacy of gamma globulin in the prevention of homologous serum hepatitis. They conclude that gamma globulin from some pools of human plasma contains protective factors against strains of infectious (epidemic) hepatitis and perhaps also against strains of serum hepatitis. Since many preparations of gamma globulin did not contain the protective substance, and since experimental hepatitis has not been regularly prevented by the use of this material, it is improbable that the administration of gamma globulin can be regarded as an effective device for the prevention of hepatitis in individuals who have received pooled plasma It is of interest, therefore, that these same investigators in a second paper have described a

technique for the inactivation of hepatitis virus by the ultraviolet irradiation of icterogenic serum and plasma (180). If these observations can be confirmed and extended, and commercial techniques for their application developed, it may again be possible to use these valuable materials without hazard.

Interest in mumps has been enhanced as the result of work carried out during and since the recent war. Enders and his associates (181) confirmed the earlier studies of Findlay & Clarke (182) and Johnson & Goodpasture (183) that this disease could be produced in the monkey by the inoculation of the virus in Stinson's duct. These investigators also showed that emulsions of parotid glands from infected monkeys could be used as antigens in the complement fixation test and that skin hypersensitivity to virus contained in suspensions of the parotid gland could also be demonstrated in persons who had recovered from mumps. This problem has been greatly simplified by the demonstration by Habel (184) and Levins & Enders (185) that mumps virus could be propagated in the chick embryo.

The Henles (186) have studied the antigenic nature of virus present in the embryo and have shown that there is one reactive substance fixed to the virus and another which is soluble in the embryonic fluids. Complement fixation tests with these materials have proved to be of considerable value in the diagnosis of such later complications of mumps as meningeal encephalitis or orchitis in the absence of known preceding or concurrent parotitis One recent study by these workers is of interest (187). Artificial inoculation of embryo-propagated virus was made in children in whom no complement fixing antibodies were demonstrable and who were, therefore, believed to be susceptible to infection Several of these subjects developed typical mumps associated with a good antibody response. One developed orchitis without parotitis Most important, however, was the fact that 8 of 15 children exposed in this way developed a brisk immunological response in the absence of any evidence of clinical mumps Furthermore, virus could be easily isolated from the saliva of these children at about the time when a clinical disease might have been expected to be present. It is evident, therefore, as predicted by earlier epidemiological studies, that inapparent mumps is exceedingly common and that such missed cases may well transmit the disease.

*Rickettsial disease*—Two rickettsial diseases have gained prominence in the last few years. One of these, Q fever, was originally discovered among packing house workers in Australia in 1935 The etiological agent was isolated and designated as *Rickettsia burneti*. Later, the same agent was isolated from ticks in the Montana area and laboratory infections occurred Later, outbreaks among troops stationed in northern Italy, Greece and Corsica were observed and isolated cases were described in Panama, Switzerland and the United States. In 1946, an explosive outbreak of Q fever occurred in Texas among the employees of certain packing houses, and in 1947 the disease was discovered to be prevalent in California The disease occurs as acute febrile illness of moderate duration which may not be distinguished readily from many other febrile disorders Not infrequently a diffuse pneu-

monia occurs, under which circumstances the disease is likely to be regarded as an example of primary atypical pneumonia. Diagnosis is possible by isolation of the organism or by the demonstration of the development of complement fixing antibodies during the course of the illness. Agglutinins to the X strains of *Bacillus proteus* are not evoked in this disease and the Weil-Felix test is of no assistance (188, 189).

Successful treatment of this disorder with aureomycin has been reported (51). Response is not as dramatic as is the case when this drug is used in the chemotherapy of other rickettsial diseases.

Rickettsial pox, a previously unknown disease of rickettsial origin, was first recognized in New York City in 1946 in the course of investigation of an epidemic of an exanthematous disease. Present information in regard to this disorder has been reviewed by Greenberg (190) It is characterized clinically by the appearance of an initial lesion somewhere on the body followed in three to seven days by the acute onset of illness with fever, headache, backache, and finally by a generalized papulovesicular rash. The entire course from the onset of the initial lesion to recovery is about three weeks

An extensive laboratory and epidemiological study by the New York City Department of Health in cooperation with the United States Public Health Service led to the isolation of the infectious agent, *Rickettsia akari* The disease was transferred by the bite of mites that inhabited mice resident in the buildings where cases had occurred. Precise clinical diagnosis is not difficult if the initial lesion can be discovered. In the absence of this sign it may be confused with a number of other exanthematous diseases. Specific diagnosis is possible only by demonstration of increasing titres of complement fixing antibodies or by the isolation of the agent from the blood. The Weil-Felix test is of no value Specific therapy has not been undertaken since the disease is self-limited, mild, and not associated with serious complications or death.

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# DISEASES OF THE GASTROINTESTINAL TRACT

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## INTRODUCTION

In undertaking a review of the diseases of the gastrointestinal tract, one is immediately aware of the great advances which have been made in knowledge of these diseases and in their management. In the relatively recent past, a diagnosis was based on the history and physical examination and, although the experienced physician could acquire astuteness in recognizing and interpreting deviations from normal, he was confronted with the fact that symptoms common to benign disorders usually initiated the most serious diseases of the gastrointestinal tract, and recognition of the latter came too often in their advanced stages with consequent hopeless prognosis for the patient. The difficulties involved in establishing an early diagnosis were chiefly due to the fact that the physician could not obtain proof to support his diagnosis except by surgical exploration.

Handicapped as the physician was without diagnostic procedures to clarify the situation, the application of roentgenology to diseases of the gastrointestinal tract became one of the great contributions to medicine. The debt owed to roentgenology for the detection of disease before definite clinical signs and symptoms are manifest is immeasurable, and of equal importance has been the development of endoscopy The mere fact that this method of examination provides direct vision of those lesions which are within the range of present instrumentation has opened a field of the widest possibilities, not only in diagnosis, but in the treatment of certain conditions The place of biochemistry, in its relationship to disturbed function of the gastrointestinal tract, particularly the liver and pancreas, is becoming more and more essential and the chief concern at present is understanding the clinicopathologic significance of variations of apparently normal values The relationship of psychosomatic medicine and psychiatry to disorders of the gastrointestinal tract has been given such emphasis that some physicians and laymen have come to consider the neuropsychic phase as causative of disease, peptic ulcer and chronic ulcerative colitis in particular While daily clinical experience lends support to this conception, actual proof of psychogenesis in man is difficult, if not impossible Naturally, in the present state of knowledge, such a conception has its opponents. They are of the opinion that its proponents confuse a phase of the disease with the cause, although they do not minimize the importance of treatment of this phase, and that the psychosomatic factor should not be considered etiologic in the inflammatory lesions of the digestive tract, particularly the intestinal tract However, treatment

of the patient both for the nervous influences at work and the local disease is advised, and such combined measures are of the greatest importance.

## THE ESOPHAGUS

### Diaphragmatic Hernia

Diaphragmatic hernia until relatively recently was recognized only infrequently but it is now known that it is a fairly common condition. Kirklin & Hodgson (1) stated that "diaphragmatic hernias of all types were encountered in *1 to 2 per cent of all gastro-intestinal roentgenologic examinations.*"
The etiologic factors of diaphragmatic hernias have been reviewed by Shanks (2). He first pointed out the infrequency of the true congenital thoracic stomach and that in the great majority of cases diaphragmatic hernia is acquired. Apparently all authorities agree that the major cause of hiatal hernia is the loss of tone of the tissues in and around the cardia associated with advancing age At the Mayo Clinic, 92 per cent of the patients who have hiatal hernias are more than 40 years of age. Any condition increasing *abdominal pressure may be a contributing factor Esophagitis and ulceration* may give rise to cicatricial changes with resultant shortening of the esophagus and herniation of a small portion of the cardial end of the stomach.

The various types of diaphragmatic hernia acquired after birth have been classified by Harrington (3), who pointed out that esophageal hiatal hernia represents at least 95 per cent of the cases seen These are of the following types· (*a*) congenital short esophagus with thoracic stomach, (*b*) hiatal esophageal *hernia with shortened esophagus,* (*c*) esophageal hernia, and (*d*) para-esophageal hernia through the esophageal hiatus.

The symptoms of diaphragmatic hernia are somewhat difficult to evaluate because they change with increase in the size of the hernia and the age of the patient, and they also may be associated with other lesions in the thorax or in the upper part of the abdomen Harrington (3), for example, has pointed out that in a series of 320 cases in which surgical repair of the hernia was carried out, an average of three previous erroneous clinical diagnoses had been made before the corrrect diagnosis was established The severity of symptoms is definitely related to associated complications, particularly traumatic ulcer and incarceration of the stomach. The similarity of symptoms of diaphragmatic hernia to coronary disease is now well known and has been described by Dack and others (4), but the latter should be definitely excluded before an operation for the hernia is carried out.

Kirklin & Hodgson (1) stated that in approximately 75 per cent of diaphragmatic hernias less than three inches (about 8 cm ) of stomach lies above the diaphragm, and in 20 per cent three to five inches (about 8 to 13 cm.) of stomach is involved. *Esophagoscopy in diaphragmatic hernia is exceedingly* important, in the detection of erosions and superficial ulcerations,

and Harrington (3) stated that it should be carried out in every case of hiatal hernia in which operation is to be undertaken. The co-ordinated use of

at the cardia may be difficult to detect roentgenographically when associated with esophageal hiatal hernia [Mailer (5)] and esophagoscopy is used primarily when doubt exists after all other methods of examination have been carried out. Fortunately, the results of surgical repair are excellent. The majority of surgeons prefer the abdominal approach, although some favor the transthoracic approach.

## STOMACH AND DUODENUM

### Gastric Secretion

Some of the numerous current investigations concerning the physiopathology of gastric secretions and their important bearing on diagnosis, organic disease, treatment, and prognosis are reflected in the contributions of van Eck (6), Ricketts and associates (7), Comfort *et al* (8), Kahlson (9), and Grossman *et al* (10) Van Eck has devised a new procedure which in his judgment obviates the disadvantages of the usual test meal Ricketts and co-workers reported further observations on the role of peptic activity in pathogenesis and the course of peptic ulcer, especially with reference to the significance of achlorhydria Comfort and associates (8) have demonstrated the subnormal state of gastric secretory functions before the onset of carcinoma in a study of 277 cases The evidence which they presented lends support to the hypothesis that atrophy of the gastric mucosa plays an important role in the depression of secretory activity before the development of gastric carcinoma. Kahlson (9) suggested that impulses from the brain, mediated by the vagi, cause the liberation in the pyloric mucosa of some agent carried by the blood stream which stimulates gastric glands to secrete acid juice. Recent work of Ivy and associates (10) suggested that histamine and gastrin are identical gastric secretory hormones

Recent observations on the mucolytic enzyme, lysozyme, are of interest. It has been shown to be present in the stomach and bow

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(11) is

agent of mucosal ulceration. Grace and associates (12) found that the concentration of lysozyme in the colons of normal subjects increased in response to situational threats provoking anxiety and apprehension, and during periods of anger, hostility, and resentment. However, it was found that the increase was not great or sustained and was probably of little importance to the subjects' welfare That lysozyme is not the result of intestinal ulceration, in the opinion of these investigators, was deduced by finding it in high concentration in stools of patients who had no intestinal ulceration.

## Peptic Ulcers

*Incidence.*—The prevalence of peptic ulcer, especially duodenal ulcer, in the adult population throughout the civilized world and the important role it plays in the cause of disability and death is the subject of a statistical review by Sandweiss (13). He showed that ulcer occupies tenth place as a cause of deaths from chronic disease in the United States, and that more than 375,000 individuals consult physicians each month because of disorders arising from this ailment.

*Etiology.*—In regard to the cause of ulcer, current emphasis is placed on the psychosomatic factor and corrosion from acid gastric juice. Gastric ulcer predominates among the fisher folk in a group of Norwegian islands (Vesteraalen) north of the Arctic Circle. As a result of his investigations there, Schanke (14) concluded that gastric ulcer was probably the result of chemicomechanical and duodenal ulcer largely of neuropsychic factors

*Diagnosis*—Proper diagnosis today should be possible in more than 90 per cent of the patients and is essential to successful treatment. Althausen (15) properly observes "that the diagnosis of peptic ulcer should not be made lightly . . . because it places on the patient the burden of a fairly exacting dietary and medicinal regimen and may require far-reaching reorganization of his life."

*Medical management.*—The trend from surgical to medical management of uncomplicated duodenal ulcers has been evident for the past two decades. Up to that time the percentage of patients with duodenal ulcer operated on was almost 40, whereas at present less than 15 per cent are operated on. For various reasons, treatment currently advocated for duodenal ulcer is medical in the majority of cases, surgery being reserved for use in those cases in which medical treatment fails or in which recognized surgical complications arise While the medical treatment for duodenal and gastric ulcer is identical, the ever present menace of actual or potential carcinoma in the latter (proved to be as high as 15 per cent) must be borne in mind (16) As a result, the percentage of patients with gastric ulcer who are operated on is four times greater than those with duodenal ulcer

In the treatment of any gastric lesion, the physician should be on his guard and should suspect malignancy in the presence of certain symptoms and signs which may be summarized as follows recent onset of symptoms in an elderly patient, large size of lesion, location of lesion on the greater curvature or the prepyloric area—to a less extent exclusively on the anterior or the posterior wall [microscopic evidence of malignancy is found in 10 per [illegible] 18 per cent of prepyloric ulcers, and

of gastric contents at intervals of 10 to 15 min ; early pyloric obstruction; increase in size of lesion during course of adequate treatment, or early recurrence of lesion following such treatment; persistence of occult blood in

feces when a controlled diet is given; presence of meniscus sign, and a gastroscopic appearance of elevated lesion, its edges or rim blending with mucosa, the irregular floor being brownish red, violet, gray or dirty color, perhaps containing nodules, nodes or ridges.

Progress in treatment has been characterized by the introduction of aluminum preparations, continuous intragastric drip, Meulengracht's principle of prompt and frequent feedings after hemorrhage (18), protein hydrolysates, the psychosomatic approach, and probably vagotomy. While innumerable "cures" have always been suggested for ulcer which even today range from pituitary "snuff" to fresh cabbage juice, the majority of discerning physicians subscribe to the principle of a bland, soft, and nutritious diet devoid of chemical, mechanical, and thermal irritation, frequent feedings, doses of currently approved antacids, temporary use of sedatives and antispasmodics, physical and mental rest, and other auxiliary measures, including hospitalization, whenever indicated. Theoretic considerations imply hyperirritability of the dorsal vagus nucleus. The effect following successful bilateral vagotomy emphasizes the importance of the cephalic phase of gastric secretion in such patients. The important fact is that the medical management of peptic ulcer, duodenal ulcer in particular, has been successful directly in proportion to the degree in which the acid gastric juice has been neutralized during the entire 24 hr Successful surgical treatment is largely based on the same premise.

Recent observations having a bearing on treatment and its outcome are worthy of consideration. Kirsner, Levin & Palmer (19), in confirmation of the investigations of other well-known authorities, have demonstrated that excessive nocturnal gastric secretion is characteristic of duodenal ulcer. Voegtlin (20) has called attention to the difficulty of reducing the nocturnal acidity by the usual methods, but that healing may proceed nevertheless. Batterman & Ehrenfeld (21) have demonstrated the advantages of aluminum hydroxide in combination with magnesium trisilicate.

The reports of Raimondi & Collen (22), Flood (23) and others disclose unsatisfactory results of ulcer therapy. Raimondi & Collen stated that two-thirds of all patients had had recurrences at the end of the first year, while Flood stated that only 48 (21 per cent) of 233 patients with duodenal ulcer followed for an average of 5 9 years remained continuously free from significant symptoms. This leaves an uneasy feeling that the treatment was inadequate in many respects provided that proper selection of patients was made

*Prevention of recurrence*—Many contributions in recent years by prominent gastroenterologists have dealt with this phase of the ulcer problem, which has not been stressed sufficiently in the past. Whether we regard ulcer as a separate disease, as the manifestation of a chronic local disease, or a general systemic derangement, the patient as a whole must be encompassed in our therapeutic planning This, apart from a complete physical inventory, presupposes tactful inquiry into the psychosomatic and environmental aspects and into personal habits and mode of eating. In addition,

the baneful influence of emotional tension, physical fatigue, respiratory infections, alcohol, tobacco, condiments, caffeine-containing beverages, stimulating or coarse foods, and hurried, improper mastication must be stressed The institution of a protective regimen during periods of stress is an essential precaution. Continued co-operation with respect to diet, medication, and hygiene is usually achieved only by fully acquainting the patient with the nature of his disease and with the rationale underlying his treatment. There is much justification for the old adage: "Once an ulcer patient, always an ulcer patient." The tendency for the patient to throw off all restraint after he has experienced comfort for several weeks or longer must be zealously guarded against; otherwise recurrence is in the offing.

*Surgical management.*—Surgical treatment of uncomplicated duodenal ulcer is now relatively rare since it is accepted that the chief indications for surgery are for complications of duodenal ulcer and for patients who are refractory to medical treatment. Until recently there has been general agreement as to the surgical principles to be followed, namely, that since subtotal gastrectomy brings about the most profound modification of gastric function, particularly in its secretory activities, the operation offers the best protection against recurrence of ulceration. It should be kept in mind, however, that when patients are carefully selected, gastroenterostomy will sufficiently diminish secretory, motor, and sensory activity to be followed by excellent results and it is the only operation which has ever been devised for duodenal ulcer which is entirely reversible. The results of the most commonly performed procedure for uncomplicated duodenal ulcer today, namely, subtotal gastrectomy, are excellent in the great majority of cases [Gray & Williams (24)], although ulceration does recur in a small percentage of cases.

The disagreeable symptoms of the so-called dumping stomach may follow gastrectomy. Accumulating evidence supports the contention of a number of investigators and clinicians that disturbances of carbohydrate metabolism are not responsible for this postgastrectomy syndrome. In spite of the current conflicting opinions as to the mechanisms involved in engendering these disturbances, it is generally accepted that the rapid intake of food into the jejunum is somehow responsible. Machella (25) recently reported the results of investigations on 16 patients manifesting symptoms of the dumping stomach. He concluded that the early symptoms of this postgastrectomy syndrome were due to distention of the jejunum by the fluid which enters the lumen of the gut in response to the presence of hypertonic solution and not to distention by the mechanical presence of the food *per se* In his opinion, the condition is not caused by hyperglycemia, although this may be present during a period of symptoms. He stated that the symptoms may be prevented by the administration of atropine in physiologic doses before meals but not by bilateral vagotomy

The surgical management of uncomplicated duodenal ulcer was more or less agreed on, namely, subtotal gastric resection or gastroenterostomy in selected cases, until Dragstedt and his associates (26) proposed bilateral

vagotomy. Although this procedure is not new, Dragstedt deserves great credit for the most thorough experimental and clinical study of the physiologic and clinical effects of vagotomy in the treatment of peptic ulcer. In the short period of time since he published his clinical results, many reports of the experience of others have become available. In Alvarez's review (27), for example, more than 200 articles pertaining to this subject were cited; and recently, the American Gastroenterological Association, through its committee on vagotomy, assembled the results in 3,000 cases in which vagotomy was performed by surgeons in this country (28).

Of first importance in vagotomy is the completeness with which the operation is carried out Many anatomic studies, therefore, have been made of the distribution of the vagus. Walters and co-workers (29) have described several variations in the distribution of the vagus, and also explained some of the difficulties encountered in accomplishing a complete division of all the trunks.

The pertinent questions concerning vagotomy have been expressed by Moore and his associates (30) and from the study which this group of observers made they reached the following conclusions.

> Patients who have had other surgery, such as pyloroplasty, posterior gastrojejunostomy or gastric resection, and who present themselves with renewed ulceration are ideal subjects for this procedure The previous surgery does not in any way complicate the operation, and it may be carried out with excellent relief of symptoms in cases in which renewed attack on local structures through the abdomen would be technically complicated, with the end results open to question.
>
> The largest group of cases in which this procedure seems to be of value is that of young or middle-aged men with a long history of peptic ulceration, possibly with previous perforations or hemorrhages, unobstructed and not acutely bleeding, who have been refractory to careful medical therapy and who have severe ulcer pain in times of stress, which can be relieved transiently by the usual antacid, milk or food. This type of patient, in our experience, obtains a uniformly good result from this procedure, but the duration of the relief is at present unknown.

Since that time, experience has shown that vagotomy alone does not achieve all that is desired, particularly in respect to ensuring satisfactory gastric motor function Colp and his associates (31) have commented on the recent practice of adding gastroenterostomy to vagotomy by stating that in their opinion gastroenterostomy combined with bilateral infradiaphragmatic vagotomy is the preferred procedure in cases of duodenal ulcer in which subtotal gastrectomy is unsuitable. While subtotal gastrectomy still remains the operation of choice in duodenal ulcer, they have combined it with infradiaphragmatic vagotomy in a series of cases in which preoperative acidity was high and there was a tendency to bleed. The operative mortality has not increased, but the postoperative morbidity attributable to the added vagotomy has increased slightly Whether the incidence of recurrent gastrojejunal ulceration will be diminished remains a subject for further study.

In the meantime those who have had much experience in observing the

results of vagotomy seem inclined to postpone a wide application of the operation until the late results can be known. If vagotomy does bring about permanent relief to patients with jejunal ulcer following gastroenterostomy or partial gastrectomy, it will be one of the great contributions to surgery.

*Complications: (a) Hemorrhage.*—Management of acute gastrointestinal hemorrhage due to gastric or duodenal ulcer is still a perplexing problem and becomes even more so when no lesions can be identified. The decline in mortality from gastrointestinal hemorrhage in the past decade, especially with nonoperative measures, is attributed largely to liberal transfusions of blood and early feeding which combat shock, tissue anoxia, development of often irreversible and eventually fatal dehydration, hypoproteinemia, and acute malnutrition and places the patient in a much stronger position to withstand further hemorrhages. The continuous drip method of transfusion introduced by Marriott & Kekwick (32) in 1935 in England is deservingly well regarded by Jones (33) and other British authorities. Factors which have a more serious prognostic bearing in general are advanced age, large size of lesion, associated degenerative processes of any of the body systems, or complications, for example, acute perforation. Marked elevation of the blood urea nitrogen is regarded as a serious omen. Failure of improvement within 48 hr. after having been placed on a strict regimen or occurrence of initial hemorrhages while under such regimen is justification for surgical interference without unnecessary delay by some authorities. By and large, bleeding from a deep, indurated gastric or gastrojejunal ulcer is usually more profuse and hence more dangerous than from a duodenal ulcer. Indiscriminate operations on patients in whom the cause of hemorrhage has not been ascertained are unwise, for in 16 to 20 per cent of such patients objective evidence of a gross chronic gastric or duodenal lesion will not be demonstrable.

It is generally conceded that the conventional criteria are inadequate in providing timely information as to the actual amount of blood lost, as to whether the patient is still bleeding and if so to what degree, in short as to immediate prognosis. Hence the tendency in recent years to advocacy of measures other than simple laboratory ones and clinical rules of thumb which can be variously interpreted. Bennett, Dow & Wright (34) in 1942, for example, recommended the serial determination of plasma and blood volume, and others, like Costello (35), procedures of somewhat similar nature Mortality statistics of medically treated gastrointestinal hemorrhages from ulcer are exceedingly difficult to evaluate but are probably fairly represented by Barnes' figures quoted by Gordon-Taylor (36). He said that 3.5 per cent of patients less than 50 years of age and 13 4 per cent of patients more than 50 years die

The surgical management of acute gastrointestinal hemorrhage from ulcer is becoming better defined in so far as the indications for emergency operation Evidence seems to warrant the belief that surgical intervention is in the best interest of the patient who is more than 45 or 50 years of age in whom massive hemorrhage has occurred from a previous ulcer and when the

bleeding persists after 48 hr. Such management requires that the general condition of the patient be sustained by every means including adequate replacement of blood and that subtotal gastrectomy with the removal of the lesion be undertaken when the operation is reasonably feasible It is safe to predict that this procedure will be more frequently carried out in selected cases since the risk of subtotal gastrectomy is so small among competent surgeons (less than 5 per cent). Among patients who have recovered from massive gastric hemorrhage and in whom the presence of an ulcer is proved, the indications for operation are fairly definite. If pain of ulcer continues and is difficult to control, operation can be justifiably advised. If a second hemorrhage occurs, particularly when the patient is beyond middle life, operation should be carried out. Holman (37) has recently formulated a policy for the management of those patients who have recovered from the hemorrhage which had necessitated hospitalization. He showed that more than 50 per cent of these patients will bleed again, a few fatally, and that 75 per cent will have symptoms that require medical attention. All of these are potent arguments for surgical treatment. The results of surgical management indicate that recurrent bleeding can be anticipated in less than 5 per cent of cases after gastric resection, while in less radical procedures the rate of recurrence is much higher.

*Complications· (b) Perforation.*—Clinical and experimental observation has shown that a small perforation of an ulcer, a duodenal ulcer in particular, when the stomach is relatively empty may not prove serious. Taylor (38) has shown that early perforations will seal themselves if the stomach is emptied and kept empty by aspiration and that the gastric contents in the peritoneal cavity will be sterilized and absorbed if the leakage is not gross and if the contamination is not repeated. Of a consecutive series of 28 patients with perforations that Taylor treated by this method, 24 recovered. Of the four deaths, three were not related to the conservative method of treatment Bingham (39) reported a successful outcome in a patient so treated and listed the indications and contraindications. This method of treatment should have its greatest usefulness when the patient is inaccessible to skillful surgical care, as may occur at sea or in the hinterland.

In the surgical management of perforation of ulcer, either gastric or duodenal, evidence is accumulating that subtotal gastrectomy has been more advantageous than closure of the perforation. The experience of European surgeons is indicated by the review of Bobbio (40) who reported a series of 29 cases in which partial gastrectomy was carried out without mortality [illegible]

the stomach, and it offers the maximal safeguard for the future of the patient. However, circumstances frequently dictate that the procedure of choice is simple closure of the perforation. Surgical treatment of the ulcer is then carried out at a later date, if it becomes necessary.

## Recurrent Ulcer: Surgical Management

No surgical procedure carried out for ulcer will give absolute assurance that ulceration will not recur. The surgical management of such recurrences represents a most serious problem for both the patient and for the surgeon. In recurrent ulcer following gastroenterostomy, it is fortunate that the *jejunal ulcer can be promptly and permanently dealt with by disconnecting* the jejunum from the stomach. In recurrent ulcer following the most commonly performed operation today, namely, subtotal gastrectomy, the problem is a much more complicated one, but vagotomy as has been pointed out may be a great aid in dealing with the situation both in respect to dealing with the ulcer and in preventing its recurrence All authors agree that operations for recurrent ulcer should *not be undertaken until every effort is made* to control the situation by medical management [Eusterman & Balfour (41)].

## Tumors

*Nonmalignant.*—It is important to draw attention to the fact that various types of benign tumors may be responsible for a chronic anemia without symptoms referable to the digestive tract and to emphasize the danger of overlooking them by neglecting roentgenologic or gastroscopic studies which will readily disclose them. These tumors are satisfactorily removed by operation with prompt correction of the anemia

*Malignant*—Cancer of the stomach continues to be one of the great problems confronting the medical profession because of the difficulties of early *diagnosis [Ogilvie (42), Welch & Allen (43) and Wangensteen (44)] which is* chiefly responsible for the continued high percentage of patients with inoperable lesions. Of the more recent approaches to earlier detection of cancer of the stomach, those carried out by St. John and co-workers (45) and Rigler (46) are of interest. These investigators conducted routine roentgenologic examinations of the stomach in apparently normal individuals. St. John and his co-workers examined 2,413 patients roentgenologically and three were found to have unsuspected malignant gastric tumors. In the Rigler series of 544 symptomless persons more than 50 years of age who had normal secretory activity, there were discovered three who had carcinoma and 19 who presumably had benign polyps.

Another development toward early recognition concerns the cytologic study of gastric secretion for evidence of carcinoma cells. Papanicolaou (47) in 1946 and Cooper *et al* (48), Fremont-Smith and co-workers (49), and Andersen and co-workers (50) have reported their investigation on this subject. The last named group reported on carcinoma of the esophagus and cardia. In spite of some inherent difficulties, it appears that cytologic examination of secretions may prove to be of real value in the diagnosis of gastric carcinoma.

The present status of the surgical management of malignant lesions of the stomach is unfortunately not conspicuously different from what it has

been for several years. There has been a steady though slow increase in the resectability rate chiefly due to the safety with which the more extensive resections including total gastrectomy can be carried out. For instance Walters, Gray & Priestley (51) reported that in 1947, 125 gastric resections with eight deaths, a mortality rate of 6 4 per cent, while 19 total gastrectomies were done in that year with one death, a mortality rate of 5.3 per cent. That this is an evidence of particularly careful selection of cases is probable, for in 1948, 174 partial gastrectomies were done with 12 deaths, a mortality rate of 6.9 per cent, while 26 total gastrectomies were done with four deaths, a mortality rate of 15 4 per cent.

Whether the more radical procedures will increase the over-all percentage of permanent cures is doubtful, but at present the surgeon has no other course to follow than to remove a malignant process of the stomach if it appears that restoration of gastrointestinal continuity can be carried out in healthy tissue; consequently, total gastrectomy is being performed much more frequently. This fact along with the extensive resections done for benign lesions has led to renewed interest in the clinical and experimental studies related to the ultimate effects of radical or total gastrectomy. Although Waugh & Fahlund (52) have pointed out that individuals can live in a fairly satisfactory state of health in so far as nutrition and well-being are concerned, MacDonald, Ingelfinger & Belding (53) recently have shown that in their own experience and in a review of the literature a high incidence of macrocytic, hyperchromic anemia was found in patients surviving total gastrectomy for three or more years. In the experimental animal, there is still considerable uncertainty as to the effects of chronic malnutrition or possibly some metabolic deficiencies on the expectation of life, and many factors are involved in evaluating this problem. In experimental total gastrectomy, one of the important investigations concerns the estimation of uropepsin in the urine and its relation to the secretory level of activity of the stomach. The reports of Bucher & Ivy (54) and Balfour, Preston & Bollman (55) are of significance.

## HEPATOBILIARY SYSTEM

### The Liver

The unprecedented accumulation of literature in the past decade bearing on the various aspects of the biliary tract, the liver in particular, has been due to a number of factors Chief among these was the revival of interest in the etiology, nosology, and treatment of cirrhosis; the development, general application, and appraisal of tests of liver function; the pandemic of viral hepatitis during World War II; the prevalence of its congeners, homologous serum and inoculation hepatitis, and increasing resort to needle biopsy of the liver in more recent years Moreover, the exposure of countless numbers of our service personnel to diseases prevalent in the tropics has made necessary increasing familiarity with hepatic disorders or complications, the result of amebiasis, dysentery, malaria, schistosomiasis, and leishmania-

sis. Needless to say that because of these various impelling factors and the publicity given them, knowledge in this large field has been greatly extended.

The marked advances made in the treatment of hepatic cirrhosis has largely been the result of investigations demonstrating that hepatic injury is related to certain nutritional deficiencies The effectiveness of a nutritious diet supplemented by vitamins of the B complex group was demonstrated originally by Patek & Post (56), and amply confirmed subsequently by Snell (57) and others. Patients treated in this manner had a longer survival period, and in many cases there was presumptive evidence of arrest of the disease process. The familiar high protein, high carbohydrate, and low fat regimen has been modified in recent years by the addition of more generous amounts of fat to increase the daily caloric requirements so essential for malnourished patients. Such modification was recommended and carried out in the treatment of both the acute and chronic forms of hepatitis without demonstrable detrimental effect. Many investigators have produced experimental cirrhosis in animals by diets which were low in protein and high in fat, or by greatly reducing all lipotropic factors The addition of these factors, choline, cholinecystine, or methionine prevented hepatic injury. Notwithstanding, there exists today a marked divergence of opinion as to the efficacy of lipotropic agents in the treatment of cirrhosis in man. The recent conclusions of two pioneer investigators in the field of dietary hepatic injury, Gyorgy and Goldblatt (58), are of interest:

> It is questionable whether with all these dietary factors the etiology of massive hepatic cirrhosis is completely defined. The interchangeability of sulfur-containing amino acids (cystine, methionine) and vitamin E as leading etiologic factors makes it difficult to accept pure deficiency as the basis of massive hepatic cirrhosis.

Snell (59) has summarized our present knowledge concerning etiology, natural history, and early recognition of portal cirrhosis. MacMahon & Thannhauser (60) observed five patients who had xanthomatous biliary cirrhosis with respect to etiology, symptomatology, gross and microscopic pathology, and characteristic changes in blood lipids. Their contribution brings knowledge of this rare and eventually fatal disease up to date.

The all important role of the detoxicating function of the liver is generally recognized If the liver extracts with potent antitoxic properties have been developed, then it is reasonable to presume that gratifying progress has been toward fuller understanding of hepatic physiology and more effective methods of treatment. In Nasio's recent article (61) mention is made of the pioneer investigations of Japanese workers with respect to yakriton and of the American investigators, Forbes and his associates (62) on Forbes' antinecrotic principle. According to Nasio, the crystallized principle necrotin developed by his countrymen has a more general antitoxic effect and is devoid of unfavorable reaction. The author's remarkable claims as to the effectiveness of necrotin awaits confirmation by others.

*Acute icteric and nonicteric viral hepatitis and their sequelae*.—The wealth

of contributions with reference to the symptomatology, pathology, and treatment of acute viral hepatitis has familiarized physicians with these aspects of the disease. Of most concern at this time are the nature, and in particular, the incidence of such sequelae. That acute viral, as well as other forms of acute hepatitis, can progress to fatal acute and subacute necrosis, postnecrotic cirrhosis (nodular hyperplasia), and portal cirrhosis is universally conceded, but there is marked difference of opinion as to the frequency with which such significant sequelae occur.

*Present status of tests of liver function.*—The medical profession is interested in tests of hepatic function for two primary reasons, first, as an aid in estimating the general state of function of the organ, and second, as an aid in the differential diagnosis of jaundice. In the presence of jaundice, our chief aim is to differentiate intrahepatic from obstructive jaundice, that is, a medical from a surgical jaundice. The greatly increased surgical risk to the patieint with hepatitis and the humiliation consequent on mistaken diagnosis and procedure need no comment.

The major circumstances constituting the difficulties of a differential diagnosis may be recapitulated briefly as follows: intrahepatic changes, such as those of acute and chronic hepatitis or biliary cirrhosis; cholangitis in association with, or as a complication of, gallstones, postoperative stricture, or choledochitis; intrahepatic arrest of bile flow giving rise to obstructive phenomena in cases of acute and subacute forms of hepatitis and cirrhosis, as emphasized by Steigmann & Popper (63); painless jaundice from a stone in the common duct, especially in the presence of complete occlusion of the duct, which happily is infrequent; painful or colicky types of pancreatic carcinoma with incomplete obstruction of the common duct; acute hepatitis simulating acute cholecystitis, or those instances of cirrhosis giving rise to biliary colic in the complete absence of stones or other abnormalities of surgical nature.

The present status of tests of hepatic function, in a simple practical form, has recently been outlined by Butt (64). His contribution also contained numerous references to the important current literature, especially that of American investigators, who have particularly distinguished themselves in this field Tests which may be used as aids in differentiating intrahepatic and obstructive jaundice in Butt's opinion are the bilirubin, alkaline phosphatase, urobilinogen, Quick prothrombin time, and thymol turbidity tests and duodenal drainage In the absence of jaundice, tests for retention of bromsulfalein dye and cephalin-cholesterol flocculation and thymol turbidity tests are indicated Butt properly admonished that none of these tests are without their limitations and that they should be carried out by competent technicians and always be interpreted in conjunction with other laboratory and clinical findings in the individual case

*Needle biopsy of liver* —In the past, abdominal exploration or peritoneoscopy has been employed frequently in order to clarify the difficult diagnosis As such procedures have inherent advantages, they will be carried out from

time to time although increasing resort to needle (punch, trocar) biopsy is evident. Recent contributions by Sherlock and associates (65, 66) in England, Haex (67) in Holland, Volwiler & Jones (68), Schiff and his associates (69), Stauffer (70), and other investigators in this country attest the expediency and safety of needle biopsy even when the intercostal approach is employed. Complications following such biopsy are minimized by the proper selection of the patient, estimation of prothrombin time [upper limit 24 sec., Quick (124)], availability of facilities for transfusion, co-operation and at least semi-alertness of the patient during the intercostal approach, and careful supervision for 24 hr. after this maneuver.

While the advantages of needle biopsy cannot be denied, mention should be made of the fact that not infrequently there is difficulty of proper histopathologic diagnosis even when one or more specimens are obtained from a representative area A combination of needle liver biopsy and studies of hepatic function has been employed by Hoffbauer, Evans & Watson (71), Volwiler & Elliott (72), Mateer and his associates (73), and others at home and abroad. While the results from these combined studies by no means always parallel each other, they are nevertheless most illuminating. It is obvious that such a combined procedure, plus thorough clinical study, represents distinct progress in the diagnosis and treatment of hepatobiliary disease

*Treatment of massive hemorrhage from esophageal and gastric varices primarily due to hepatic disease*—While splenectomy, and more recently injection of esophageal varices with sclerosing substances, frequently have been followed by cessation of bleeding, the ultimate results in the main have not been satisfactory. Massive hemorrhage will recur in about 50 per cent of the patients who have been submitted to splenectomy and the mortality rate in such postsplenectomy bleeders will approach 100 per cent. Hence the advocacy by Whipple (74) and Blakemore (75) of more direct procedures, namely splenorenal or portacaval shunting operations for attaining the primary objective, reduction of portal hypertension The current concept of the causes underlying portal hypertension in congestive splenomegaly and the operation of choice in given circumstances are described in an article by Rousselot (76). Womack (77) pointed out the seriousness of portal hypertension of intrahepatic origin, as well as the difficulty of assessing the extent of liver damage by the usual tests of liver function He especially stressed the hazardous nature of the various types of operations proposed, singly or in combination.

Since rupture and bleeding from the esophageal varices are the primary cause of death in so high a percentage of patients with hepatic cirrhosis, the use of sclerosing solutions in their treatment has given some encouraging results in the hands of Crafoord & Frenckner (78), and Moersch (79). The most direct method of management in so far as removal of the varices is concerned is that of Phemister & Humphreys (80), who carried out transthoracic esophagogastric resection in cases in which splenectomy and obliter-

ation of the varices by injection had failed to control the tendency to hemorrhage. In Womack's opinion the indication for such radical procedures is impending death from massive hemorrhage due to esophageal varices, and the indication for such surgery is most definite when such emergency confronts a patient with compensated function of the liver.

## Gallbladder and Ducts

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are concerned with dyskinesia or dyssynergia, persistence or recurrence of painful manifestations following cholecystectomy, and determination of the optimal time for operation in cases of acute cholecystitis

The past and current literature on dyskinesia reveals considerable uncertainty and difference of opinion as to the mechanism involved and, as a consequence, the nature of the treatment advocated. However, Schondube (81) and Chiray & Pavel (82) have agreed that a hypertonic state, causing spasm of the vesical neck and of the sphincter of Oddi, is the underlying disturbance. In the opinion of the last two well-known investigators, other causes for functional disturbances in the gallbladder and ducts are cholecystatony, vesical hypertonia, and insufficiency of the sphincter of Oddi Undoubtedly painful manifestations of functional nature occur in these structures in psychoneurotic individuals, just as they do in the stomach and colon, and this possibility should always be kept in mind, particularly in the absence of objective evidence of organic nature

Although the various organic conditions that can give rise to painful, persistent, or recurrent symptoms after cholecystectomy for bona fide cholecystic disease are known, the fact remains that in a considerable number of patients undergoing a second operation the findings are negative or inadequate in so far as accounting for the symptoms presented. This is an indication of the serious diagnostic difficulties that may beset us The usual roentgenologic and laboratory procedures are of little avail under the circumstances. Stones in the duct, for example, are not revealed by routine roentgenologic examination Tests of pancreatic function may be revealing. Wilkinson (83) reminded the medical profession of a means of diagnosis too often neglected, namely, diagnostic transduodenal biliary drainage, which in the experience of well-known clinicians and surgeons is often the sole means of revealing the presence of cholangitis, choledochitis, or stone in the common duct, to say nothing of contributing dependable evidence concerning the nature of jaundice, when it is present Miller and his associates (84) and Levyn & Meyers (85), among others, have placed much reliance on this procedure

*Differential diagnosis of benign and malignant forms of obstructive jaundice.*—As a rule, the differentiation between benign and malignant obstructive jaundice should not be difficult If routine diagnostic procedures do not per-

mit of satisfactory diagnosis, duodenal drainage, quantitative determination of urobilinogen in feces and urine, and certain tests of pancreatic function should be employed. Calcium bilirubinate and cholesterin crystals in the duodenal content are suggestive of the diagnosis of stone in the duct. The presence in it of blood is an indication of carcinoma. The association of normal pancreatic function tests and blood is an indication for the diagnosis of carcinoma of the ducts or papilla. Jaundice due to stone is rarely accompanied by complete obstruction of the duct, so that persistent values of less than 5 mg of urobilinogen per day in feces or the finding of only traces of urobilinogen in the urine are rare in jaundice due to cholelithic obstruction. Obstruction due to carcinoma, however, is almost always complete, so that the amount of urobilinogen in feces is less than 5 mg. per day, as a rule, and the urine contains no urobilinogen, or only mere traces.

*Medical management* —By and large the nonsurgical treatment of organic cholecystic disease is limited, in our opinion. However, medical management seems indicated under certain circumstances. Treatment is usually of an individualized nature and includes a high fat, bland diet in the absence of stones or history of colics or obesity; the removal of all foci of infection; administration of oxidized bile salts, saline aperients, especially in constipated individuals and antispasmodics, and continuous duodenal (medical) drainage for late postoperative cholangitis, hepatitis, or choledochitis. Occasionally, use of nitrites and mild sedatives is indicated.

*Surgical management.*—The general principles followed today in the surgical management of disease of the gallbladder and ducts are well standardized and accepted [Maingot (86) and Cole (87)]. The silent gallstone, the "acute gallbladder," and postoperative stricture of the common duct are worthy of comment. Comfort, Gray & Wilson (88), Graham (89), Berk (90), and Zollinger & Cutler (91) reported their observations on 112 patients in whom asymptomatic gallstones were found incidentally during the course of abdominal operations. Follow-up data on these patients for 10 to 20 years revealed that indigestion supervened in 30, biliary colic in 21, and both jaundice and colic in five. The remainder, which is exactly half of the total, remained asymptomatic. The authors concluded that surgical treatment of the silent gallstone may be classified as optional or elective However, operation should not be postponed after symptoms develop, especially after colics occur.

The management of acute cholecystitis was discussed by Graham (89), Berk (90), and Zollinger & Cutler (91). Although mindful of the possibilities of such serious complications as empyema, gangrene, perforation, and the frequently resulting, rapidly fatal peritonitis, these authorities have observed that the majority of the patients respond to conservative measures, so that operation may be deferred for 48 hr. or even for five or six days

*a third of the patients die of the immediate consequences, and another third* from operative intervention for repair of the injury. Although the remaining third make good immediate recoveries after such intervention, recurrence of biliary complications may prove fatal eventually. The repair of such injuries is, to say the least, a major surgical problem. When the common duct is mistakenly divided during cholecystectomy, immediate repair of the injury by end-to-end anastomosis is usually followed by satisfactory results. If, however, the injury is not recognized at the time, an entirely different and tragic situation confronts the patient and the surgeon. Many procedures for the repair of such injuries have been advocated by Walton (93), Walters (94), Cole, Ireneus & Reynolds (95), Lahey (96), Cattell (97), and Turner (92). Walters (98) and his first assistants, in a recent survey of 186 cases of stricture of the common duct, in which Walters performed various procedures, found that the late results were good in 58 per cent of the cases. The best results were obtained in cases in which the *hepatic duct was anastomosed to the duodenum, and when sufficient com*mon duct was present above the stricture to anastomose it accurately to the duodenum Good results have been obtained in an average of 80 per cent of these cases; whereas in an average of 52 per cent of cases in which the ends of the duct were anastomosed, good results have been obtained. In the four patients in which both the hepatic ducts were anastomosed to the duodenum, the patients were well and without biliary obstruction two, three, eight, and eight years, respectively, after operation. Maingot (86) gave a splendid review of the indications for these procedures and the surgical principles which must be followed to avoid such catastrophes

## The Pancreas

The pancreas continues to hold particular interest for clinicians, surgeons, physiologists, and biochemists because of the realization that there is much still to be known about the significance of impaired function and because all the pathologic conditions that occur in the organ may be overlooked very easily in their early stages Measures for the detection of these still leave much to be desired. The pancreas has been slow to yield up its secrets for various well-known anatomic and physiologic reasons.

*Tests of pancreatic function; present status*—The reliability, in fact, indispensability, of the comparatively simple and accurate amylase and lipase tests, especially the former, in the diagnosis of acute pancreatitis is generally recognized. Too often failure to realize that use of the tests is indicated or delayed recourse to them impair their effectiveness. If physicians were mindful of Elman's admonition (99) that the pancreas should always be considered as the cause of severe pain in the upper part of the abdomen, and if the determination of amylase in the serum were carried out at the height of the attack, or at least within 48 hr. of the onset, present failures to use these tests would be decreased to a minimum The pioneer investigator, Lagerlöf (100), has observed more recently that elevation of the serum amylase and

lipase also may occur in acute biliary disease, in duodenal ulcer with involvement of the sphincter of Oddi, acute perforating ulcer with perforative peritonitis, and in pancreatic carcinoma He also has observed high elevation of the serum amylase for as long as 24 hrs. following injection of morphine or gallbladder colic which he respectively attributed to transient contraction and increased tone of the sphincter of Oddi, resulting in stasis of contents in the pancreatic duct The method of determining the amylase in the urine contains elements of error so that this test is not as accurate as the blood amylase test However, the test for the amylase in urine, like determination of the level of serum lipase, may prove of value in the later stages of an acute attack.

The simplicity, accuracy, and dependability that characterize laboratory tests for the detection of acute pancreatitis are frequently lacking in tests employed as diagnostic aids in cases of pancreatitis after the acute phase has passed, as well as in cases of chronic sclerosing pancreatitis and pancreatic carcinoma. The conventional tests up to recent years were those concerned with the qualitative determinations of the excess fat and undigested muscle fibers in feces, the quantitative determination of fecal fat and nitrogen, and tests for sugar in the bile and urine, and the tolerance for dextrose. The roentgenologic examination for evidence of calcification in the gland was also a supplementary routine procedure.

With the elaboration and refinement of secretin, the secretogogue effect of mecholyl chloride and the development of the Agren-Lagerlof (101) double-lumen tube, direct examination of the duodenal content for volume, pH values, and concentration and total excretion of bicarbonate and enzymes has been made possible, according to Comfort (102). At present, opinion is divided as to the diagnostic value of tests of pancreatic function. This is apparent in the observations of Bauman & Whipple (103), Sjoberg (104), Pratt (105), Dozzi & Bokus (106), and Löffler & Essellier (107). Dornberger, Comfort, Wollaeger & Power (108) recently analyzed the duodenal contents in 28 cases of proved chronic pancreatitis before and after stimulation with secretin and their appraisal of this procedure is contained in the following statement:

> The secretin test has a definite but limited place in the diagnosis of chronic relapsing pancreatitis Determinations of value for total volume, concentration of bicarbonate and total bicarbonate are the important parts of the test rather than the values for enzymes. Twelve patients with proved chronic relapsing pancreatitis without any of the sequelae, such as diabetes, steatorrhea, or calcification of the pancreas were studied with the secretin test during the interval between attacks when the serum enzyme values were normal Presumptively abnormal values for volume and bicarbonate or bicarbonate alone disclosed disturbance of external pancreatic secretion in seven of the twelve patients.

This same group of investigators (109) carried out intake-excretion studies for total fecal solids, fat, and nitrogen in 20 cases of chronic pancreatitis which yielded information of definite diagnostic value.

*Acute pancreatitis.*—The etiology of the disease is still a controversial matter. The common channel theory is unacceptable to many investigators. Clinically there are two distinct pathologic types. The commoner type, acute edematous pancreatitis (acute interstitial pancreatitis), is manifested by a boggy, swollen pancreas with fluid under tension and may be accompanied by fat necrosis It usually subsides spontaneously if left undisturbed. The other type, acute pancreatic necrosis (acute hemorrhagic pancreatitis), is a serious disease with dissolution of a large part of the organ. In the first type, operation is not required; in the second, it must be seriously considered Because of the greater incidence of the first type, the high mortality rate attending early operation (52 to 78 per cent), and the failure of the necrotic process to be arrested by operation, as revealed at necropsy, there has been a general advocacy of conservative treatment for the past decade on the part of physician and surgeon alike. Differentiation of the two types must be based on the patient's clinical appearance and progress Shock, which is seldom seen in edematous pancreatitis, should be considered an indication of acute pancreatic necrosis. Another indication is manifestation of spreading perforative peritonitis. A third is failure of the disease to subside If symptoms and signs persist, suppuration of the pancreas should be suspected. On the basis of animal experimentation, Popper and co-workers (110) concluded that vasomotor changes may be responsible for transition from edema to pancreatic necrosis and that the extent of such changes determine the degree of pancreatitis.

The physical, chemical, and pathologic changes that may occur during an attack of acute hemorrhagic pancreatitis is mirrored in an investigation conducted by Gambill and his associates (111) This study revealed disseminated fat necrosis within and without the abdominal cavity, generalized peritonitis, ascites, bilateral hydrothorax, diabetes mellitus, hypoglycemia, hypopotassemia, and uremia The evidence tends to support the belief expressed by Edmondson & Fields (112) that the concentration of calcium in the serum may be of prognostic value in acute pancreatitis

The conservative treatment consists of a variety of measures From the standpoint of drug therapy Elman (99) recommended sublingual administration of glyceryl trinitrate (1/1,000 grain) and repetition of the dose in a few minutes shortly after the onset of the attack. This measure often results in dramatic cessation of the attack. If the seizure has been underway for a number of hours, the drug is ineffective. Circulatory stimulants and atropine to decrease pancreatic secretion and to counteract irritation of the vagus and vascular spasms have been recommended. Popper and co-workers (110) also suggested the administration of papaverine for its vasodilating effect. Tetraethylammonium chloride (Etamon) has recently been recommended for the relief of pain. It is administered intravenously in doses of 5 cc. for the first few days. As the attack subsides, intramuscular injections of 3 cc. may be sufficient. Other measures consist of glucose with insulin or adrenocortical extract given by phleboclysis, suction with the Wangensteen appara-

tus, transfusion of blood plasma, administration of amino acids to correct hypoproteinemia and of vitamin K. Sulfonamides or antibiotics are useful in the necrotizing type. The presence of gallstones obviously is an indication for their surgical removal at some subsequent favorable period.

*Chronic pancreatitis.*—Elman's researches in acute pancreatitis have done much to stimulate interest in, and familiarity with, the symptoms, signs, diagnosis, and treatment of this disease. The investigations of Comfort, Gambill & Baggenstoss (113) in chronic relapsing pancreatitis without associated disease of the biliary or upper part of the digestive tract of sufficient degree to influence the clinical picture have had a similar effect with respect to the chronic form. For instructive details concerning this comparatively unfamiliar, usually unrecognized although rather frequent disorder, this contribution should be read in its entirety. The diagnosis of chronic relapsing pancreatitis should be made with a high degree of accuracy because of the characteristic clinical picture, including painful exacerbations and disturbances of function of the pancreas demonstrable during and between acute exacerbations. Since the publication of this article in 1946, a number of contributions on this subject have appeared which in whole or large part confirm the authors' conclusions. In 1948 Gambill, Comfort & Baggenstoss (114) published their observations in 27 cases of chronic relapsing pancreatitis associated with disease of the biliary tract. Briefly stated, the purpose of this study was to determine whether chronic relapsing pancreatitis was the same or a different disease when disease of the biliary tract was associated. The results of this investigation, when compared with the series of 29 cases unassociated with disease of the biliary tract, disclosed many similarities and remarkably few dissimilarities.

Results of conservative surgical procedures (internal and external drainage of the biliary tract and of pancreatic cysts, pancreatolithotomy or gastroenterostomy for duodenal obstruction) are sufficiently good to warrant frequent and early use Radical surgical procedures (partial or total pancreatomy) may be used if conservative ones fail and then only for relief of persistent and disabling pain. Medical measures include (*a*) diet and replacement therapy (insulin and pancreatin) for control of diabetes and steatorrhea, (*b*) drugs for control of pain, and (*c*) supportive measures in case of shock.

*Relief of pain in pancreatic disease*—Observations on the use of glyceryl-trinitrate and tetraethyl ammonium chloride in the relief of pain of acute pancreatitis have already been made. The recurring protracted, often intense, pain of chronic relapsing pancreatitis frequently leads to morphinism or alcoholism, or both. Relief of varying degree may be obtained by the injection of the posterior splanchnic nerves with a solution of 0 75 per cent [illegible] remove the thoracic sympathetic chain between the ninth and twelfth thoracic ganglions. In carcinoma of the pancreas this procedure is rarely

carried out on account of the patient's general condition and the curtailed life expectancy. Deep roentgen therapy is sometimes effective in relieving pain.

*Carcinoma of the pancreas.*—From a clinical diagnostic standpoint the disease may be classified into two types, the icteric and nonicteric. Bard & Pic's first modern review of the disease in 1888 (116) emphasized jaundice, distention of the gallbladder, cachexia, and loss of weight as the predominant symptoms. This conception held sway for the past half century, but in the past nine years a number of American authors have rightly stressed the significance of pain rather than of jaundice in pancreatic carcinoma.

Almost 20 years ago Eusterman (117) reported observations on 533 jaundiced patients for whom the diagnosis was confirmed by operation or necropsy. In 84 per cent of the 69 cases of pancreatic carcinoma, the primary diagnosis was correct and in 8 per cent the alternate diagnosis was correct. This makes a total of 92 per cent of cases in which the correct diagnosis was made with the aid of the few diagnostic tests then available. Thus, contrary to the opinion of some current writers, the diagnosis of carcinoma of the pancreas should not be difficult in the presence of jaundice.

Jaundice may be absent in from 20 to as high as 50 per cent of patients who have carcinoma of the pancreas at the time medical advice is sought. Under such circumstances, the correct diagnosis is still too frequently missed by the physician and surgeon, no matter how experienced and alert he may be. This is particularly true in the absence of palpable pancreatic tumor, palpable distended gallbladder, or both. This difficulty was confirmed by a clinical study by Eusterman & Wilbur (118) of 88 verified cases in 1933. They found that roentgenologic studies of the stomach, duodenum, and colon provided valuable information in about half of these cases in which such studies were carried out. Dashiell & Palmer (119) reported almost identical results in this respect

Comfort, Parker & Osterberg (120) noted an appreciable elevation of the content of lipase in the serum in about 37 per cent of a series of cases, but secretion of enzymes was diminished In the absence of obstruction of the common bile duct and pancreatic duct, a circumstance that would obtain in carcinoma of small size in the body or tail of the organ, the diagnostic value of laboratory tests was found to be negligible.

*Surgical management*—Until relatively recently, surgical procedures on the pancreas have been restricted to such conditions as pancreatic cysts, stones, and acute pancreatitis. The recognition of carcinoma of the islands of Langerhans continues to pose an exceedingly difficult diagnostic problem. It is generally conceded that even though surgical exploration of the pancreas is carried out, an adenoma or carcinoma of the islet cells is not always demonstrable and definitely incriminated as the cause of a patient's spontaneous hyperinsulinism and associated hypoglycemia.

Although many attempts were made to remove portions of the pancreas, particularly the head, it was not until 1935 when Whipple, Parsons & Mullins

(121) reported a successful resection of the duodenum and head of the pancreas for carcinoma of the ampulla of Vater that the extraordinary development of radical operations on the pancreas began. The most striking evidence of this development has been the fact that total pancreatectomy is now an established surgical procedure, for it has been shown that the entire gland may be removed (for carcinoma, calcification, or chronic pancreatitis), and the remarkable fact is that reasonably good health and nutrition are maintained without replacement therapy except for insulin (122).

Priestley, Comfort & Sprague (123) have recently reported a follow-up study of a patient five and a half years after a total pancreatectomy for islet-cell carcinoma This patient has remained in essentially good health Her diabetes has continued to be relatively mild as compared to the type of diabetes which commonly occurs in children, adolescents, and young adults In spite of the loss of large amounts of nitrogen and fat in the feces, she was able to maintain a satisfactory nutritional state The values for blood lipoids and serum proteins remained within the normal range, and there was no abnormality of the functions of the liver which were measured, in spite of the fact that her diet had not been supplemented with choline, lecithin, or other lipotropic substance

In so far as radical surgery for carcinoma of the pancreas is concerned, *although it is too early to make predictions concerning cures and to compare* results with those of palliative procedures of biliary enteroanastomosis, it is reasonable to hope that general principles of the surgical treatment of cancer will become applicable to pancreatic carcinoma.

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# DISEASES OF THE CARDIOVASCULAR SYSTEM (MEDICAL)[1]

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## Methods of Clinical Investigation

The last decade has added enormously to available techniques for the direct study of the human heart in health and disease. Angiocardiography and cardiac catheterisation continue to yield a rich harvest of new ideas. It has now been realised that a catheter inserted in a pulmonary artery to the point of blockage affords a measure of pulmonary capillary pressure, normally 7 to 15 mm Hg (1). This pressure is raised in mitral stenosis and in left heart failure.

Fluoro- or electrokymography is reviewed (2). The method records optically the movements of chosen parts of the edge of the cardiac silhouette. The method has been used to demonstrate prolongation of the isometric phase of ventricular relaxation in pathological hearts (3)

Owing to the inconvenience of the direct Fick (catheterisation) technique of determining cardiac output, particularly for repeated studies at intervals, other and simpler techniques have been checked against it. A pulse pressure technique in dogs was found to correlate very closely ($r = 0.936$) with the results from the Fick method (4). The Fick method and the dye injection technique were also found to correlate closely (5, 6) The dye method permits approximation to the mean pulmonary circulation time, and if the cardiac output is known the volume of blood in the lungs may be estimated In normals this is about 700 to 1,000 cc. (6), but strangely enough it is said that this volume changes very little with the degree of heart failure This is a surprising result which requires critical reconsideration.

Starr & Mayock (7, 8) report on the significance of abnormal forms of the ballistocardiogram. The normal W shaped complex with a tall middle peak (J) and smaller downward peaks I and K is normally symmetrical. Rounding, flattening, and notching of I and J waves are abnormal. Hypertensive heart disease is less likely to produce abnormalities than other etiological varieties Examples are given illustrating various types of abnormality such as a flattened or notched J wave in left ventricular aneurysm

Prinzmetal and his colleagues (9) have now developed radiocardiography. By means of a specially constructed ink-writing Geiger-Muller counter this method records graphically the passage of radioactive blood through the heart chambers. A carefully shielded Geiger-Muller tube is placed over the

[1] This review covers the period from January, 1948 to June, 1949.

heart and the counts emitted by radiosodium passing through the heart are recorded as rising and falling curves of concentration. The dose (0.1 to 0 2 millicurie of radiosodium) is rapidly injected into a vein at the elbow with special attention to the avoidance of any lag in the systemic veins. In normal subjects a peak of concentration is recorded over the right ventricle within 2 to 3 sec. A lower peak follows some 5 to 7 sec. later over the left ventricle This peak falls away slowly in a further 5 or 6 sec. Tracings are shown of the delay which occurs in cardiac failure and also of the excessively rapid circulation found in thyrotoxicosis. This method is clearly a great refinement on previous methods devised for the study of circulation time.

In the midst of these esoteric procedures it is healthy to think again of the almost forgotten technique of percussion of the heart. Stroud and others (10) percussed within 10 per cent of the radiographic transverse diameter of the heart in 75 per cent of 333 examinations, while Levin & Nagel (11) were within 1.5 cm. of the heart size in 80 per cent of the cases. Parkinson (53), however, expresses considerably less confidence in percussion

## Heart Failure and its Treatment

The complex changes which occur in association with cardiac failure are the subject of much intensive investigation (12 to 17). A rise in venous pressure may occur often with a normal or high cardiac output (18, 19) and, to account for this rise, mechanisms of increased venous tone (16), fluid retention, and increased blood volume (20) are invoked. Raised venous pressure alone is no longer adequate to account for edema (21). The importance of sodium retention by the kidneys has been emphasised (22, 23, 24). Increased elimination of sodium, induced by mercurials (22) and aminophylline (25), or a negative salt balance from a low salt intake lead to marked improvement in cardiac edema. The large volumes of water recommended in the Schemm régime (175) are adversely criticised by Newman & Stewart (26). The mechanism of sodium retention and the part it plays in the production of edema are still uncertain, however Kattus and others (27) have shown that similar reduced excretion of sodium takes place during exercise in normal subjects Recovery may take place from congestive failure with no increase in glomerular filtration rate (15) Increased venous pressure affecting also the renal veins may determine water and salt retention as a secondary consequence (28) Biorck and others (29) report reduction of serum albumin in cardiac failure with restoration to normal with recovery.

Studies of the pulmonary circulation in health, heart failure, and emphysema are reported (30, 31). During exercise in normal subjects the lung blood flow can be greatly increased without any rise in pulmonary arterial pressure. The pulmonary vascular pressures generally are raised with the lung congestion of left heart failure, during exercise the cardiac output cannot rise and may even fall, the pulmonary vascular pressure rises still higher if heart failure is induced by exercise (30, 31).

*Cardiac glycosides.*—Bloomfield *et al.* (32) report that ouabain increases

right ventricular pulse pressure and cardiac output in heart failure often with little significant change in venous pressure. McMichael (33) has reported similar effects and notes that they differ from the action of digoxin in which venous pressure reduction is a notable accompaniment of clinical improvement. Venous pressure fall was also noted with great regularity following lanatoside C in heart failure (34). The possibility of quantitative differences in the action of digitalis and strophanthus is raised. The stimulating action of ouabain in heart failure is clearly demonstrated, and digoxin probably has a similar though less pronounced action This and other recent work (17, 35) suggests that venous pressure reduction after digoxin may be a secondary rather than a primary effect of the drug

Venesection often has a remarkable action in increasing the output of the failing heart, possibly by reducing a diastolic over-distension of the failing chamber (36). Similar clinical improvement with increased cardiac output may follow the use of veratrum viride (37), which lowers pulmonary arterial pressure as well as systemic arterial pressure, perhaps thereby unloading the failing hypertensive heart. Tetraethylammonium bromide (TEAB) reduced the arterial and venous pressures in hypertensive heart failure with temporary clinical improvement (38, 39).

Theophylline isopropanolamine has been shown to increase the output of the failing heart for a short time, this action being accompanied by reduction in filling pressure of the right side of the heart (40). This action was more prominent in ischaemic than in rheumatic heart disease, a point which has been noted previously (41)

Pugh & Wyndham (42) have shown that mercurial diuretics have a "venesection like" action lowering venous pressure and increasing cardiac output in heart failure This action may result from blood volume reduction during diuresis These observations may add point to the rationale of the régime recommended by Gold (43) for the cardiac invalid An intramuscular dose of 0.5 to 2 cc. mercuhydrin sodium solution is given daily in addition to digitalis preparations and dietetic measures Excess fluid is removed and the patient restored to a low "dry" weight.

## Diseases Affecting the Heart

*Constrictive pericarditis*—Tuberculous infection of the pericardium is probably the cause of most cases of constrictive pericarditis, as 16 of 18 cases finally developed the latter condition in the healing stage (44). Paul, Castleman & White (45) review their experience of constrictive pericarditis, and though admitting a tuberculous origin as likely indicate that it is often difficult to prove histologically. In one type of constrictive pericarditis the left ventricle may be particularly embarrassed and a sequence of manifestations like those in mitral stenosis with enlargement of the right ventricle may follow (46) Semple (47) also notes the resemblance to mitral stenosis in some cases Cardiac catheterisation indicating elevated pulmonary vascular pressures is helpful in diagnosis of this left ventricular constriction (46). Tubercu-

lous pericarditis is far more frequent in males than females (44, 48), and it is often associated with infection of other serous cavities (polyserositis) (44). It may often be difficult to get bacteriological proof of tuberculous infection from examination of the pericardial fluid (47). In some instances of constrictive pericarditis the heart may be enlarged (45, 47). Tuberculous pericarditis has a high mortality (44) In the early stages it may be extremely difficult to diagnose: constitutional symptoms are mild, there may be little dyspnoea, and there is a stage in which venous congestion is slight. Sometimes pericardectomy may be necessary even in the presence of active disease (44).

*Rheumatic heart disease.*—Sokolow found electrocardiographic changes in 147 of 700 cases of rheumatic fever (49) and emphasised the importance of serial electrocardiograms Conduction defects (atrioventricular block and intraventricular block) were the most important Borderline prolongations of PR interval (0.22 sec ) might be indicated by shortening of PR with recovery T wave changes in the absence of pericarditis were next in frequency. Abnormal rhythms came next, but auricular fibrillation was rare. The abnormal QT/TQ ratio in rheumatic fever is favourably influenced by oxygen administration (50) Kuttner & Markowitz (51) made an important study of the significance of a mitral systolic murmur in rheumatism. When the murmur was loud and blowing 48 per cent of the patients studied developed organic heart disease 5 to 19 years later, while in those with a soft systolic murmur only 13 per cent developed unequivocal heart disease. In the former group there was also a high percentage of rheumatic relapses Master (52) also emphasises the importance of a loud systolic apical murmur in the diagnosis of organic mitral insufficiency and discusses the differential diagnosis. An excellent general review of the radiology of rheumatic heart disease is given by Parkinson (53).

Calcareous aortic stenosis has been studied retrospectively on clinical and pathological records of 107 cases (54). The maximum incidence is in the seventh and eighth decades Cardiac failure in this group is very resistant to treatment Cardiac pain was recorded only in nine patients A clinical diagnosis was only made in 24 per cent of the cases. The condition should be suspected with a systolic murmur only at the aortic area and the diagnosis checked by x-ray screening or by tomography (55). Horan & Barnes' series (56) showed anginal pain in 28 out of 100 cases, while in Davies & Steiner's 14 patients (55) angina occurred in eight It is said that coronary sclerosis which is commonly associated with calcareous aortic stenosis is less severe in those with gross aortic stenosis (56)

Calcification of the mitral valves in osteitis deformans with extension into the interventricular septum and consequent heart block is described by Harrison & Lennox (57)

*Other cardiac conditions.*—Rachmilewitz & Braun (58) note in typhoid fever T wave changes which are reversed by daily doses of nicotinic acid Evans (59) describes a condition of cardiac enlargement of obscure etiology with various arrhythmias and finally heart failure It may be familial or may

arise *de novo*. Fibrosis of the myocardium often with intracardiac thrombosis and perhaps a slight excess of glycogen in the myocardial cells is found post-mortem. The name "Familial Cardiomegaly" is proposed. It seems doubtful, as yet, if this enlargement can be clearly separated from some other forms of cardiac failure of uncertain causation.

Ballinger (60) draws attention to cardiac failure resulting from amyloid infiltration of the myocardium and reports two cases. The condition of fibroplastic parietal endocarditis with eosinophilia may be illumined by the report of Lennox (61) of an acute parietal endocarditis associated with status asthmaticus and eosinophilia. This may well merge with other "allergic" diseases of the heart.

The variety of remedies suggested for terminating paroxysmal tachycardia continues to grow. Youmans *et al.* (62) recommended 0 5 mg. neosynephrine intravenously in supraventricular tachycardia, the rapid rate being stopped by reflex cardiac inhibition elicited by the blood pressure rise Herrmann & Hejtmancik (63) continued to use quinidine, morphine, and magnesium sulphate.

*Pulmonary heart disease*—Pulmonary heart disease is reviewed (64). In miners' pneumoconiosis the heart becomes more vertical and the outflow tract and pulmonary artery enlarge. Electrocardiographic signs of right heart stress develop (65, 66).

Erfan & his colleagues (67) describe the syndrome of pulmonary endarteritis due to bilharziasis The ova produce a pulmonary endarteritis with resulting obstruction to blood flow. Apart from dyspnoea and weakness, giddiness and fainting were common symptoms There were signs of pulmonary hypertension and right heart stress Polycythaemia was absent

The importance of low oxygen tensions in the lung alveoli in producing local vasoconstriction and pulmonary hypertension is further confirmed by Dirken & Heemstra (68) Lowering the oxygen tension in one lung reduces the local circulation, diverting the blood through the opposite lung.

## ELECTROCARDIOGRAPHY

Various methods of obtaining the unipolar and precordial electrocardiogram have been studied and compared Bryant, Wilson & Johnson (69) have examined records with and without 5,000 ohm resistances in the arms of the central terminal; they conclude that 10 per cent of the records show significant differences and that resistances in the arms of the indifferent electrode should be large if inaccuracies are to be avoided. Rappaport & Williams (70) have investigated the problem theoretically and consider that an error is introduced by omission of the resistances and no advantage gained. They recommend the Goldberger technique for limb leads in combination with the Wilson central terminal complete with the resistances.

Kisch (71) has investigated the validity of the augmented unipolar limb leads and has shown that the zero potential against which these leads are taken differs for each extremity in the same person. Such leads are not uni-

polar leads, which might more correctly be termed "1 to 2" standard leads. By immersing volunteers in a swimming pool and establishing an indifferent electrode in the surrounding medium it has been shown that the Wilson central terminal is not consistently at zero although it is more indifferent than an electrode on any fixed point on the body surface (72) Most authors agree that CF leads may be misleading. A committee set up by the British Cardiac Society (73) has recommended the general use of V leads and the discontinuation of other methods.

Sokolow (74) has stressed the value of unipolar extremity leads Pathological Q waves, significant slight ST-T depressions, and left bundle branch block (LBBB) are sometimes seen in VL without changes in the precordial leads.

The electrical doublet theory has the virtue of simplicity and is widely used to explain the electrocardiogram. Ventricular excitation is considered to pass from endocardium to the epicardium with an electrical "source" followed by a negative "sink." However, studies on unipolar extremity leads in the dog are not in accord with this theory (75); the QRS-T deflection is thought to result from interference between electrical events due to depolarisation in proximal and distal zones of the whole heart. Events in the proximal zone lead to a downward deflection of the beam and in the distal zone to a positive deflection. Forced extrasystoles in the proximal zone lead only to a QS form and in the distal zones to R waves. This evidence suggests that VR is not a cavity lead but derived only from interference of the proximal zone, comprising the anterior and posterior parts of the right ventricle excluding the apex, and a distal zone comprising most of the left ventricle. Similar zones, spatially oriented towards the examining electrode, have been mapped out in the dog heart for VF (76) and VL (77). Nahum & Hoff (78) have investigated the precordial electrocardiogram and found that the only force producing negativity of the QRS is in the excitation of the proximal zone of myocardium which is relatively smaller in area than the distal zone. These confusions and conflicts concerning theory will perhaps be reconciled when vector spatial electrocardiography is more fully investigated and understood. Groedel & Borchardt (79) have shown that the electrocardiogram obtained from the heart surface in patients with pneumothorax and at operation is essentially identical with that obtained on the chest wall perpendicular to the ventricle The authors also consider that precordial leads without Q waves are not pure LV electrocardiograms. An electrical exploration of the heart at pneumonectomy showed that only one pattern was found over the left ventricle and that excitation was practically simultaneous over its surface (80) These studies on direct electrocardiography have been presented in a monograph (81).

Hellerstein & Katz (82) have studied the electrical effects of injury An elevation of the ST segment is recorded at the injured surface Thus injurious pressure of a catheter tip on the right ventricular endocardium of the dog produced ST elevation of an endocardial lead and depression of an epicardial

The findings of Hecht (83) on unipolar intracardiac electrocardiography have been confirmed and amplified by others: the P wave is largely positive low down in the auricle, biphasic in the middle, and negative near the sinus node (15). The right ventricular intracardiac record starts with a positive wave (84). Groedel & Borchardt (85) explored the epicardial surface of the auricle and found progressive changes in the P wave configuration similar to those of Hecht. In fact, there are identical potential variations inside and outside the auricle although they vary from the sinus node region to the ventricular junction.

The intracavity potentials in right bundle branch block (RBBB) have been investigated (86). A second late R wave can be recorded low in the right ventricle; this corresponds with the ascending limb of the second and late R in $V_1$.

Jones & Feil (87) analysed the electrocardiograms of 54 patients who showed both normal conduction and bundle branch block (BBB). There was almost no shift in the electrical axis when abnormal conduction supervened One hundred necropsy examinations on patients known to have LBBB showed only 14 per cent with demonstrable septal lesions. Rasmussen & Moe (88) consider that there is no sharp distinction between the electrocardiogram of LBBB and that of left ventricular hypertrophy; both graphs are the result of different degrees of retarded ventricular excitation. Rasmussen & Nyhus (89) studied the development of the electrocardiogram in mitral stenosis and consider that there is a progressive retardation of right ventricular excitation leading to RBBB in 6 per cent of their cases

Improved diagnosis of chest pain has been sought in the use of anoxaemic tests. A 10 per cent oxygen mixture is generally used Burchell *et al* (90) report the results of 730 tests without fatality They point out that the degree of arterial oxygen unsaturation is not the critical factor. A negative result may be obtained in cases with severe coronary arterial disease. These tests should not be carried out in patients over 60 years of age, in those with enlarged hearts, in those with previous myocardial infarction, or in those with emphysema The standard leads are not as useful as precordial leads and of these leads CR's are probably better than the unipolar leads since the changes in the S-T segment are summated in this bipolar lead and hence more readily seen. Transient ischaemic changes, however, may be local; for this reason multiple leads are recommended for anoxic tests. The test is reported as negative in normals and 45 per cent positive in patients with typical angina (91) Blumgart (92) has wisely criticised the tendency to minimise bed rest in patients with ischaemic cardiac disease anastomotic channels develop slowly and the reduced cardiac work of rest favours healing. A group of patients with prolonged ischaemic pain which is uninfluenced by rest or trinitrin and without any objective evidence of myocardial necrosis is reported (93). The condition is described as "coronary failure." Electrocardiographic changes are often absent or minimal but may transiently resemble those of myocardial infarction An unusual case of myocardial necrosis without coronary arterial occlusion is described (94) The diagnosis was made

during life on the clinical findings and on an electrocardiogram which showed RS-T depression and no large Q waves At necropsy, subendocardial necrosis was found.

Coronary arterial disease is now well-known in young adult males. In a most extensive review of 866 cases in men under 40 with 450 necropsy records, Yater *et al.* (95) have drawn attention to the condition. The frequency of the disease increased 30 times between the first five years of the third decade and the last five years of the fourth There was a definite disposition to hypertension (although most cases would come into the range of high normals). There was hypertension in 20 per cent of the cases during the attack and in 70 per cent the blood pressure was normal within 24 hr.

A detailed correlation of electrocardiographic and pathological findings in 161 cases of myocardial infarction is reported (96), which confirms and extends the views of Wilson (176). In 20 cases of anteroseptal infarction (96) the diagnostic signs were only present in two cases on the standard leads. Precordial leads show a QR or QS in chest position 2, 3, or 4. In 57 cases of anterolateral infarction (97) the Q wave was seen further to the left. Ten cases showed an initial upstroke in $V_3$ and $V_4$. This might be due to any of the following cardiac displacement, LBBB, infarction of the left side of the septum, an unusually early record, or patchy infarction Extensive posterior infarction reduces the opposing potential and diminishes the effect of an anterior infarct on the chest leads; this reduction is shown in an analysis of 52 cases (98) with anteroposterior lesions. VF was frequently diagnostic in those with large posterior infarcts but it was negative in 23 of the total of 52 cases High lateral infarcts (99) were rarely shown on the precordial leads, Q waves were more often seen in VL. Infarction of the interventricular septum (100) occurred in 63 per cent of all the necropsies In two of these infarctions with extension from the posterior wall there was complete atrioventricular block. Levine & Burge (101) report a case of complete heart block due to septal infarction with intermittent Wolf-Parkinson-White conduction. The pathological Q waves of infarction disappear from the complexes showing aberrant conduction although RS-T changes persist. These findings may be the result of reversed ventricular excitation which is said to be initiated at the epicardial surface when conduction is through aberrant atrioventricular bundles *Logue & Whipple (102) have reported that LBBB may occasionally* revert to normal conduction on carotid sinus pressure. By this means the diagnostic Q waves in patients with suspected myocardial infarction may be revealed

Subendocardial necrosis was an outstanding feature in three necropsied cases described by Hecht & Ritzmann (103). Electrocardiograms taken soon after the onset of symptoms showed depressed RS-T segments, high voltage R waves, and Q waves were absent. There was a long history of angina pectoris in each case

The electrocardiogram of ventricular aneurysm was analysed in 15 cases (104). All showed a mainly upward QRS in VR. A normal VR may, therefore, be of negative diagnostic significance Persistent elevation of the ST-T seg-

ment has been considered to be an important feature of the electrocardiogram in left ventricular aneurysm. However, three of eight proven cases did not show this change (105).

R waves falling on previous T waves are considered to indicate a state of increased myocardial irritability (106). This abnormality preceded the development of ventricular flutter or fibrillation and, in five animal experiments, it was abolished by quinidine.

A detailed study of the time relations between the electrical and mechanical events in the cardiac cycle of man is reported (107).

Limitation of spread of thrombosis by anticoagulants is now a well established therapeutic measure in acute myocardial infarction. Their particular value in this condition has been reported (108, 109). Further spread of clotting and embolic accidents occurred in 25 per cent of 368 untreated control cases while the incidence was 11 per cent in 432 who had been treated. The mortality in the untreated group was 24 per cent and in those receiving anticoagulants 14.9 per cent.

## Congenital Heart Disease

More accurate diagnosis of congenital heart disease has become essential to the success of surgical treatment Whilst angiocardiography and cardiac catheterisation may provide valuable, and at times crucial information concerning abnormal anatomy and haemodynamics, they in no way replace the simpler diagnostic methods. A report on 60 cardiac catheterisations in various malformations shows that cardiac catheterisation was a safe procedure but failure to enter the pulmonary artery occurred in 25 per cent (110). Oximetric analysis has been used to investigate the changes in arterial oxygen saturation following inhalation of oxygen, changes in posture, and exercise (111) Cyanotic congenital cardiac patients show a greater rise in arterial oxygen than normals after breathing oxygen, exercise, however, produces an average fall of 11.2 per cent in the congenital group whilst normal controls remain unchanged

Selzer *et al* (112) have investigated the clinical findings in cases of pulmonary stenosis with patent foramen ovale They consider that this combined lesion may be recognised by the association of pulmonary artery dilatation and cyanosis with clubbing Pure pulmonary stenosis does not produce cyanosis with clubbing and in the tetralogy of Fallot the pulmonary artery is small The authors distinguish the Eisenmenger syndrome because cyanosis is less intense and pulmonary artery dilatation greater than are seen in pulmonary stenosis with patent foramen ovale However, we would consider that the distinction is not so simple as this

Green *et al* (113) analyse the reported cases of pure pulmonary stenosis and cases of idiopathic dilatation of the pulmonary artery They add a further four cases of each condition with haemodynamic studies. The arterial oxygen saturation is normal at rest in both conditions, but they may be distinguished by loudness of the second pulmonary sound in idiopathic dilation of the pulmonary artery and the finding of right ventricular hypertension in

pulmonary stenosis. Three other cases of pure pulmonary stenosis are reported (114).

Taussig (115) discusses cardiac malformations amenable to the Blalock-Taussig operation and Baker *et al.* (116) have studied 50 cases after this operation. Squatting occurred in 80 per cent of Fallot's tetralogy and mental development was generally normal. No case of Fallot's tetralogy had either a loud drum-like pulmonary second sound or a diastolic murmur. In 33 of the 50 cases there was dramatic improvement after operation.

The haemodynamics of atrial septal defects have been further elaborated. Taylor *et al* (117) find a high right ventricular output with only moderate elevation of the pulmonary artery pressure, and some cases showed a subnormal arterial oxygen saturation although clinical cyanosis is rare. Diagnosis is confirmed by finding high oxygen saturation in the right auricular blood compared with that from the venae cavae. However, this difference may be found in other conditions, including a rare abnormality described by Perry *et al* (118) in which there was a communication between the left ventricle and right auricle. Handelsman *et al* (119) have studied the circulation in five patients with isolated septal defects The degree of clinical disability was related to the development of an increase in pulmonary resistance shown by right to left shunt and elevation of pressures in the pulmonary artery. Such an increase in resistance may be due to pathological changes in the pulmonary vessels or to a rise of left atrial pressure although this is unlikely as pulmonary congestion is absent.

Rich (120) has shown that there is a tendency to develop widespread pulmonary vascular obstruction in patients with pulmonary stenosis. Twenty-one cases were studied and 90 per cent of them showed diffuse microscopical thrombi in various stages of formation and recanalisation in the pulmonary vessels.

The electrocardiographic feature of left ventricular dominance in tricuspid atresia has been reported (121, 122), and two cases with associated large atrial septal defects had a good exercise tolerance at 35 years of age.

Ninety-six cases of coarctation of the aorta are reviewed (123); the sharp drop in age incidence after 30 is attributed to early death. Hypertension was the most common presenting feature but none of 80 fundi examined showed a severe hypertensive retinopathy Twenty per cent of the cases had basal diastolic murmurs and 80 per cent had evidence of collateral circulation Pugh (124) states that a quarter of these cases have no radiological evidence of the lesion. An abnormal corrugated patch of intima below and opposite the stricture, the "jet lesion," may be responsible for unsuccessful anastomosis or for the development of a saccular or dissecting aneurysm (125). The zone of coarctation is due to thickening and deformity of the media, and the ligamentum arteriosum appears to take no part. The peripheral blood flow has been measured (126) There was no difference between normal controls at rest and 14 patients with coarctation of the aorta. After operation there was a slight decrease in blood flow in the arms and a slight increase in the legs. The femoral pulse wave was delayed in onset and rose more slowly than

in the normal (127). After resection of the coarctation and anastomosis the abnormal features of the peripheral arterial pressures return towards normality. End to end anastomosis is more successful than subclavian-aortic anastomosis in this respect.

### Hypertension and Arteriosclerosis

The problem of hypertension is discussed in numerous reviews of great interest (128 to 135). Shorr (136) indicates that the release of renin from an ischaemic kidney cannot produce sustained hypertension. A vasoexcitor ma- [illegible]

ischaemia, as the kidney blood flow and blood vessels in early essential hypertension are quite normal (134). Volhard (137) also sets aside renal ischaemia as a factor in "red" (essential) hypertension. Smirk (138) thinks it may be only one of a number of factors

Considerable interest is now being taken in the role of the suprarenals, as a result of the following evidence: (*a*) cortical hormone produces hypertension when given with salt in excessive amounts to patients with Addison's disease; (*b*) VEM does not act in the absence of the suprarenals (136); (*c*) the suprarenal cortex is either hypertrophied or contains increased lipoids in most cases of hypertension (139), (*d*) desoxycorticosterone raises the arterial pressure immediately in hypertensive but not in normal subjects (140); and (*e*) conditions of severe stress, which are thought to lead to increased discharge from the suprarenal cortex (141), produce hypertension which has been recorded in man (142) following explosion blast and in rats following exposure to continually recurring blast of a Klaxon horn (138)

Both Volhard and Smirk emphasise hereditary and constitutional factors as important Volhard thinks that what is inherited is a vascular system which shows the effect of wear and tear earlier than a normal system. He thinks increased minute volume of the circulation is an early development in hypertension and that, as a result of prolonged stimulation, the blood pressure regulating reflexes in the aortic and carotid sinus regions lose their sensitivity The gradual decrease in elasticity which takes place in an ageing aorta leads to a loss of reflex depressor tonus, and thereby an increased peripheral resistance Hypertrophy of arteries then follows, stabilising this increased resistance. Smirk (138) is against the view that anatomical thickening of the arterioles plays much part; the vessels can in fact be relaxed, since residual postsympathectomy hypertension may be reduced to normal by tetraethylammonium chloride (143)

Perera (144) emphasises the early age of onset of essential hypertension (between 20 and 30) while Platt (145) found that, under the age of 40, 48 out of 64 cases were probably secondary to other diseases, e g. pyelonephritis. Burgess (146) emphasises the generally benign character of hypertension and shows that the prognosis is good and that life is often only shortened by six or seven years from the mean life expectancy at the particular age. Blood &

Perera (147) studied 50 patients who had survived over 10 years and up to 27 years from the time of the initial diagnosis. At the onset 21 of them had had diastolic pressures ranging from 110 to 160 mm. Hg and severe retinopathy had occurred in two-thirds of the cases in the course of the disease. In some instances the fundus changes had regressed spontaneously. The difficulty of selecting cases with a bad prognosis for operations is emphasised In benign hypertension "the physician should not be guilty of adding to fear and apprehension in a variable chronic disease which is frequently compatible with decades of normal living" (148). Sympathectomy for essential hypertension is not as successful as was at one time hoped In the later follow up of his cases after five to nine years Smithwick (149) finds that the blood pressure has often risen again to preoperation levels, and 31 per cent of the patients died during this period of observation It is doubtful if any real favourable alteration in prognosis is achieved by operation Wilkins and his collaborators (150) report that the liver blood flow is increased during the first weeks after sympathectomy (indicating splanchnic vasodilatation), but in later follow-up (6 to 10 months) the blood flow had returned to the preoperation level These changes are independent of cardiac output or blood pressure alterations It appears that the central blood pressure integrating mechanism is "set at a higher level" and when vasodilatation takes place in one area of the body it is offset by further constriction elsewhere Goldring (134) is unimpressed by his experience of sympathectomy, and Evelyn and collaborators (151) found restoration of normal blood pressure in 8 per cent and completely unfavourable responses in 79 per cent of the cases studied Keith, Woolf & Gilchrist (152) found some subjective relief from surgery but only slight lowering in diastolic pressure or death rate Peet & Isberg (153), however, report a 5 to 12 year follow-up on sympathectomy for malignant hypertension with 22 per cent survival over this period Until medicine has something better to offer in this usually intractable stage surgery may still be justified

With the rice diet, Kempner (131) achieved some reduction of blood pressure in 322 of 500 patients, with striking reduction in 125 of them Goldring (134) thinks a low salt intake may reduce blood pressure for a time but on return to a normal diet the condition relapses Even temporary reductions of blood pressure, however, may have a beneficial effect on severe retinitis as illustrated, for example, by Kempner

The use of thiocyanates in hypertension has a very narrow margin of safety and is widely thought to be of little real value. Thiocyanate levels between 8 and 12 mg per 100 cc may be accompanied by weakness, depression, nervousness, dry skin, various dermatitides, nausea, vomiting, abdominal pain, diarrhoea, anaemia, and goitre Above this level still more serious effects are encountered such as loss of hair, severe central nervous system manifestations, and even death (154). In spite of all the risks a favourable report is published by Watkinson & Evans (155) Alstad (156) had a striking result in one case but less satisfactory results in most others (157). Sodium thiocyanate apparently depresses the cardiac output as much as 50 per cent

(158) possibly by sensitising the heart to potassium. "Calcium" salts are recommended to counter the toxic effects on the heart. Osteoporosis occurs in 2 per cent of the patients on thiocyanates (159). Simultaneous administration of calcium in therapeutic doses is recommended to prevent this complication.

There are numerous reports on the action of other blood pressure reducing agents in hypertension Tetraethylammonium chloride (TEAC) or bromide reduces pressure by blocking impulses in the autonomic ganglia Its effects, however, are transient. There is little effect on normal blood pressure, while in hypertensive subjects considerable falls of blood pressure are achieved, and after sympathectomy in such patients the effect is often exaggerated (38, 160, 143).

Veratrum viride is reported as a favourable therapeutic agent in hypertension (161) Dihydroergocornine is a sympathicolytic drug which lowers blood pressure and reduces heart rate (162). Hypertensive patients are more sensitive than normal subjects. The drug dilates the arterioles, cardiac output remaining essentially unchanged. Hypertensive patients, however, become resistant to dihydroergocornine after prolonged administration (163)

*Suprarenal medulla and hypertension*—Paroxysmal attacks of severe hypertension in phaeochromocytoma may be easy to recognise. When the hypertension becomes persistent diagnosis may have to be aided by the benzodioxane test, by which an epinephrine-produced hypertension is reduced (164), or through the precipitation of attacks by 0 05 mg histamine given intravenously (165). Cahill (166), however, reports a case in which benzodioxane had no effect It seems probable that norepinephrine is formed by these tumours in large amounts (167). In man norepinephrine is a much more potent blood pressure raising substance than epinephrine (168) and, in fact, the pressor effects of norepinephrine may be counteracted by epinephrine. It is even suggested that norepinephrine may play some part in essential hypertension as hypertensive subjects are excessively sensitive to its action Increased amounts of norepinephrine have been found in the urine of hypertensive subjects (169).

*Arteriosclerosis*—An excellent review by Gubner & Ungerleider (170) stresses the problem of subintimal deposition of cholesterol High pressure within the vessels is important as is also the blood cholesterol level. Young subjects with coronary disease often have hypercholesterolaemia and this may be familial (171, 172, 173) Cholesterol is absorbed by esterification with fatty acids and it may also be synthesised from acetate in the liver. Its deposition in vessel walls is not merely dependent on blood concentration but also on the rate of removal, perhaps by the vascular lymphatics. The alteration in the connective tissues which occurs with age may lead to decreased fibroblastic and lipolytic activity in the vessel wall and, hence, impaired disposal of cholesterol Steiner (174) discusses means of control of plasma cholesterol levels Three tenths of a gram of thyroid daily would lower the level, but this lowering was followed by an overshoot above the control value on cessation of the drug The association of atheroma with obesity suggested the

trial of a low fat diet with limited cholesterol intake; this diet resulted in no alteration in the level of cholesterol in the serum. While an increased ingestion of fat and cholesterol was without effect on the serum cholesterol level, there was no accompanying increase of cholesterol excretion. This observation suggested that excess cholesterol was either metabolised or laid down in the tissues. While it may sound reasonable to reduce the fat and cholesterol content of the diet, there is as yet little positive evidence of its prophylactic or therapeutic value.

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..., *Advances Internal*

# DISEASES OF THE CARDIOVASCULAR SYSTEM (SURGICAL)[1]

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Many recent developments in the field of cardiovascular surgery constitute truly brilliant achievements, and the intensive investigations and bold ingenuity characterizing some of the experimental endeavors in this area portend other contributions of equal, if not greater, importance. Indeed the growth and scope of these endeavors have been so progressive and broadened that it is manifestly impossible in a review of this nature to give more than a general idea of some of the more significant accomplishments and trends of development. For this reason, and owing to limitation of space, primary consideration has been given to certain developments in surgery of the heart and allied great vessels.

## Patent Ductus Arteriosus

Occlusion of the uncomplicated patent ductus arteriosus is now generally accepted as the only rational treatment of this congenital anomaly. Since the risk of operation is now so low [in 1947 the mortality following operation in 643 collected cases was 4.9 per cent (1) and in a similarly collected series of 509 cases reported this year it was 1.9 per cent (2 to 5)], it is also the consensus of most observers that the procedure is advisable in all patients except those older than 25 to 30 years of age who show no progressive cardiac hypertrophy or incapacitation from the fistula. Operation is also indicated in those cases complicated by subacute bacterial endocarditis, but only after prolonged intensive penicillin therapy.

The only point about which there is some disagreement in the management of this problem is essentially technical in nature and concerns the best means of occlusion. In the early cases, obliteration of the ductus was attempted by some form of ligation "in continuity" It soon became apparent, however, that this procedure was not entirely satisfactory, for in about 10 to 20 per cent of cases closure was incomplete or the fistula recurred (1, 5). Despite various modifications of this technique, there still remained a small percentage of recurrences. For this reason, Gross (5) finally evolved the technique of complete division and suture of the ductus. This proved so thoroughly satisfactory in his hands that all forms of ligation were completely abandoned

Because this procedure is technically more difficult to perform and consequently more hazardous to the patient, some have questioned the desira-

[1] This review covers the period from approximately July, 1947 to July, 1949.

bility of its routine performance. Even such an experienced vascular surgeon as Blalock (6) prefers not to section the ductus, believing that the technique he employs is effective in maintaining closure and subjects the patient to less danger of fatal hemorrhage. His technique consists of pursestring sutures of silk placed and tied at the extreme ends of the ductus between which two through-and-through mattress sutures of silk are placed and tied, and over these a ligature of umbilical tape is tied.

With increasing experience and with the development of special instruments to facilitate the procedure and to assure greater safety in its performance, the method of complete division and suture appears to be gaining favor (2 to 4, 7 to 9). This attitude has been much advanced by the ingenious clamp devised by Potts (4) for this purpose. Containing a row of fine teeth in the opposing jaws, it can be applied to the vessel without injury and without danger of slipping off, thus permitting nontraumatic and safe handling of the divided ends of the ductus Another technical improvement has been suggested by Freeman and his associates (9) and by Jones (2) for diminishing the dangers of hemorrhage during division of the ductus. This appears to be particularly useful under certain conditions, such as in an extremely short, wide ductus and in older patients with less elastic and more friable vessels. It consists of control of the components of the shunt by a clamp or ligature on the pulmonary end of the ductus and the application of a Potts-Smith clamp on the aortic side which allows adequate flow of blood through the lumen of the aorta but completely occludes the ductus opening into the aorta With both ends of the ductus thus securely occluded, it may be safely divided and sutured.

## Coarctation of the Aorta

Approximately five years have now elapsed since Blalock & Park (10) first proposed and demonstrated experimentally a method for treating coarctation This consisted in shunting the blood beyond the point of stenosis by anastomosing the left subclavian artery to the distal end of the aorta after resection of the coarctation A short time later Crafoord & Nylin (11) and Gross & Hufnagel (12) performed the first successful operations on humans, consisting of excision of the stenotic area and end-to-end anastomosis between the proximal and distal ends of the aorta. Sufficient experience has now accumulated to establish certain conclusions concerning this method of therapy and to point up others that demand further study.

Technically there is general agreement that the ideal procedure is excision and end-to-end anastomosis Unfortunately, this is not always feasible because in some cases the constriction may be too long to permit approximation of the ends after its excision or it may arise too close to the left subclavian artery. These difficulties are further magnified in older patients by extensive atherosclerosis. Under these circumstances the method proposed by Blalock & Park (10) of using the left subclavian artery to shunt blood to the aorta distal to the coarctation has been employed (13 to 19) but this procedure

has not proved entirely satisfactory (20). On the basis of his analysis of the follow-up results in 18 cases in which this was done, Shapiro (20) concludes that this procedure will be abandoned because apparently it is not sufficiently effective in reducing the load to the upper part of the body and increasing the flow of blood to the lower half This belief is supported by the physiologic studies on cardiovascular dynamics made before and after operation by Brown and his co-workers (21), who found that the degree of return of cardiovascular function toward the normal state was significantly greater following end-to-end anastomosis than after subclavian-aortic anastomosis The solution to this problem appears to be in the recent investigations of Gross and his associates (22 to 24) on preserved arterial homografts. These observers showed experimentally that aortic segments removed from donor dogs, when preserved in a proper medium, would remain viable for as long as 35 to 40 days and could be successfully used as grafts in recipient dogs. On this basis Gross and his co-workers (22 to 24) have grafted segments of preserved human aorta in nine patients following excision of the coarcted area and at the time of their report the grafted areas were still patent from three to nine months after operation

Other technical considerations have been concerned primarily with the development of instruments to facilitate the operative procedure (17, 25, 26) Of these the clamp devised by Potts (4) and discussed under the section dealing with patent ductus appears to be the most useful. For patients in whom the coarcted segment begins close to the origin of the subclavian artery, Blalock and his associates have devised a modified Potts-Smith clamp which occludes the aorta but permits some circulation through the subclavian during the period required for the anastomosis.

The development of a successful surgical attack on coarctation of the aorta has stimulated renewal of interest in the physiopathology of this interesting lesion A number of investigators have applied various methods of study before and after corrective surgical procedures to provide a better understanding of the cardiovascular dynamics of these patients and to permit greater accuracy in the diagnosis and evaluation of operative therapy. Among the most significant of these studies are those reported by the group of investigators at the Mayo Clinic and at the Johns Hopkins University. With few exceptions, notably blood flow studies, their observations were essentially similar

Using the venous occlusion plethysmograph with the compensating spirometer recorder, Wakim, Slaughter & Clagett (27) observed that the resting blood flow in the upper and lower extremities of these patients does not differ significantly from that of normal persons. These observations are in accord with those previously reported by Lewis (28) After corrective surgical treatment there was a slight average decrease of blood flow to the arms and a slight increase of flow to the legs On the other hand, Bing and his associates (19) found that the blood flow through the forearm was significantly elevated above normal and that through the legs below normal,

whereas after operation these values returned toward normal. Owing to variation in technique these apparently conflicting observations are probably not comparable and further studies are required before final evaluation can be made.

Intra-arterial blood pressure determinations by means of the hypodermic strain guage manometer showed that in the arm both the systolic and diastolic pressures were significantly elevated above normal, whereas in the leg the systolic pressure was below normal and the diastolic pressure above normal (21, 29). Somewhat similar observations were made by Bing and his associates (19) except that they noted little deviation from normal in the diastolic component in the femoral artery. Both groups of observers found that following corrective surgical treatment of the coarctation these alterations in arterial pressure tended to return toward normal.

Comparative studies of the pulse wave contours in the femoral and in the brachial (Hopkins) or radial arteries (Mayo), made by both groups of investigators, showed delayed onset of the femoral pulse wave with prolongation of the normal interval between the onset and attainment of the peak, and a broad, rounded peak and absence of the notch normally present on the descending limb, giving a characteristic "sawtooth" pattern. This configuration of the femoral pulse wave is attributed to the "damping" effect produced by the area of resistance at the aortic stricture. The fact that, following surgical removal of the coarcted segment and end-to-end anastomosis of the aorta the femoral pulse wave assumes a more normal contour, supports this explanation (21). Further support of this concept may be derived from the recently reported ballistocardiographic wave pattern, which shows a characteristic short J K stroke produced by early abrupt interruption of the flow of blood at the coarcted area. Following corrective surgical treatment of the coarctation a typically normal J K stroke was obtained (30). On the basis of these observations and calculations of peripheral vascular resistance Bing and his associates (19) came to the conclusion that the hypertension in coarctation is probably not attributable to a renal pressor mechanism but rather to the resistance presented by the stenosis and collaterals, as previously suggested by Blumgart and his co-workers (31).

## Aortic Arch Anomalies

Considerable interest has been aroused recently in malformations of the aortic arch and its great vessels since the demonstration by Gross (32, 33) that disturbances resulting from compression of the trachea or the esophagus by such anomalies may be relieved by surgical therapy. The resulting increased awareness of the possible surgical significance of these anomalies has stimulated studies directed toward wider and more accurate clinical recognition of the problem and appropriate surgical measures for the various types of anomalies that may produce symptoms (34 to 37).

The development of proper roentgenographic techniques has now pro-

vided a fairly accurate means of determining the presence and nature of these vascular malformations (38 to 40). The numerous anatomic variations of these anomalies of the derivatives of the aortic arch system which may produce disturbances of the esophagus or trachea have been described and illustrated by Gross & Ware (41) and by Edwards (42). The former authors (41) classified them into three general types: (*a*) those with a right aortic arch with several variations; (*b*) those with a double aortic arch with one or both limbs patent, and (*c*) those with an anomalous right subclavian artery arising from the left side of the arch (*dysphagia lusoria*). Edwards (42) divided them into two groups depending upon whether the ductus arteriosus takes its origin from the left or right pulmonary artery. In his opinion the significance of this classification lies in the fact that surgical therapy in these anomalies is usually directed toward either the ductus or some structure that lies on the same side of the body as the ductus. Since the ductus usually lies on the same side as the upper portion of the descending aorta, visualization of this latter structure by roentgenography may be a helpful guide to the surgeon in determining the proper side on which to perform thoracotomy.

In general, surgical therapy in these vascular malformations consists of one of the following procedures, depending upon the type of anomaly encountered: (*a*) division of the anomalous subclavian artery, (*b*) division of the smaller or atretic (usually the anterior or left) limb of a double aortic arch; (*c*) division of the ductus (or *ligamentum arteriosus*), and (*d*) dislocation of an innominate or common carotid artery

### Congenital Pulmonic Stenosis or Atresia and Transposition of Great Cardiac Arteries

For sheer brilliance of conception and technical execution the work of Blalock & Taussig (43 to 46) in devising a successful operative means of treating congenital malformations of the heart, in which there is an inadequate pulmonary blood flow, remains preeminent in the annals of cardiovascular surgery. Indeed, their considerations and observations on this subject, as presented in their original report in 1945, were so fundamental and thorough that all subsequent investigations have in large measure been merely confirmatory To be sure, much additional information has been contributed to the problem through subsequent accumulation of extensive clinical experience and intensive physiologic studies This has led to better understanding of the underlying physiologic disturbances, to greater knowledge of the anatomic variations encountered, to more accurate diagnostic methods and better selection of patients for application of treatment, and to modifications and improvement in technical procedures.

On the basis of their experience, Taussig (45) has succinctly presented the six criteria which have proved essential in the successful application of this method of therapy.

(*a*) The primary difficulty must be lack of adequate pulmonary blood flow, (*b*)

there must be a pulmonary artery to which to anastomose the systemic artery, (*c*) a systemic artery must be available for the anastomosis; (*d*) the difference in pressure between the systemic and pulmonic circulations must be sufficiently great for blood to flow from the aorta to the lungs; (*e*) the structure of the lungs must be such that the patient can tolerate the collapse of one lung and the temporary occlusion of one pulmonary artery, and (*f*) the structure of the heart must be such that it can adjust to the altered circulation.

Taussig (46) further showed on the basis of this analysis that whereas malformations of the heart with pulmonary stenosis or atresia other than the tetralogy of Fallot are amenable to this method of surgical treatment, the operative risk is greater and the results are perhaps not as good in the former types as in the latter.

The underlying principle of this method of therapy consists essentially in the shunting of blood around the point of stenosis in the pulmonary artery by the creation of an artificial ductus arteriosus. This may be done by various operative procedures, most of which were enumerated in the original report of Blalock & Taussig (43). Experience has shown that when possible the preferable procedure is end-to-side anastomosis between the subclavian and pulmonary arteries (44, 47, 48). In this connection, Blalock (44) prefers the right subclavian branch of the innominate except in patients more than 12 years of age in whom the left subclavian is employed The major technical modification of the operation was provided by Potts *et al.* (49) and Dammann *et al.* (50), who devised an ingenious clamp, which by partial occlusion of the aorta, permits blood to flow through it while side-to-side anastomosis to the pulmonary artery is being performed. Thus, with the use of this clamp the objections raised to this method by Blalock & Taussig, who included it in their original report among the possible operative procedures, were overcome. This method appears to have distinct advantages under certain circumstances (51), such as in patients in whom a systemic artery would be difficult or impossible to use Since it permits adjustment of the size of the stoma, it is especially useful in infants or small children in whom the subclavian may be too small to furnish an adequate blood flow to the lungs. Finally, it avoids the dangers of cerebral damage which may follow the use of the carotid or innominate arteries

Although great progress has been made recently in the surgical therapy of congenital heart disease, corrective procedures for many of these problems remain to be developed Intensive efforts in the experimental laboratory, however, are being directed toward them This is well exemplified by the recent report of Hanlon & Blalock (52) on their experimental observations on venous shunts as corrective procedures in complete transposition of the aorta and pulmonary artery. They were able to show that it is technically feasible to anastomose the pulmonary veins to the superior *vena cava* and thus transmit oxygenated blood to the right side of the heart, which offers a possible approach to the surgical treatment of complete transposition of the great cardiac arteries.

## Mitral Stenosis

The impetus given cardiovascular surgery in recent years has produced a revival of interest in the surgical attack upon certain types of valvular disease (53 to 55), especially mitral stenosis (56 to 58), which lay comparatively dormant since the pioneering endeavors of Cutler and his associates (59, 60) and Allen & Graham (61) approximately twenty-five years ago. Efforts have also been directed toward both creation and closure of septal defects (62 to 64) The more recent attempts concerned with mitral stenosis may be classified into two general lines of approach, one indirect and the other direct. The former includes methods designed to by-pass the auricle and mitral valve or to relieve the associated pulmonary hypertension, and the latter is a direct surgical attack upon the stenotic valve.

Attempts to shunt blood from the pulmonary vein to the left ventricle through anastomosis of a venous graft have been made experimentally but such a by-pass has functioned for only a few days (65). It seems doubtful that this line of approach will be fruitful.

The other indirect approach to this problem, i e, relief of the associated pulmonary hypertension, appears to offer greater possibilities, at least, in providing symptomatic relief from the recurring episodes of acute vascular crises within the lungs This approach is based upon the well-known fact that in patients with mitral stenosis and atrial septal defects (Lutembacher's syndrome) acute pulmonary edema rarely develops, protection being afforded by the escape of blood through the atrial opening from the left auricle to the right auricle On this basis Jarotsky (66) and O'Farrell (67) suggested that such a defect might be created surgically as a means of therapy This procedure has been performed by both Harken (56) and Bailey (57, 58) on a few patients

The obvious technical difficulties involved in such a procedure may have been overcome by the method recently devised by Blalock & Hanlon (64) and successfully carried out in experimental animals With this technique an interatrial septal defect may be created under direct vision without interruption of the circulation, with minimal loss of blood and with fairly accurate control of size The final benefits, however, to be derived from such a shunt remain open to question Even though it be done only in patients with a normal cardiac output, as emphasized by Harken (56), the eventual effects of such a shunt may be deleterious as a consequence of reducing left ventricular output and of throwing an additional burden on the right ventricle.

Following this same line of reasoning, but with a view toward a less hazardous undertaking, Sweet (68) has produced an extracardiac shunt by making an anastomosis between the dorsal segmental branch of the right inferior pulmonary vein and the azygos vein This procedure has the additional advantage that if it is subsequently determined that an excessive burden has been placed on the right side of the heart the shunt can be readily closed with little risk to the patient. Remarkable improvement following this procedure was reported by Bland & Sweet (68) in three of five patients,

satisfactory progress in one with insufficient time to warrant conclusion and death in one from severe recrudescence of rheumatic fever. Significant diminution of the abnormally high left intra-auricular pressure was observed following release of the shunt with no evidence of impairment in peripheral circulation Like the foregoing procedure the theoretic merit of this procedure is also open to question. As emphasized by Swan (69), a "circus movement" of blood is created through the right ventricle throwing an additional burden on this side of the heart in the effort to maintain left ventricular output It is possible that the consequent long term effects upon the heart would be deleterious but this is not yet known. Further observation and experience are essential for final evaluation but at present this method appears to offer some value at least in alleviating the serious episodes of acute vascular crises within the lungs

Still another surgical approach designed to relieve the associated pulmonary hypertension by diminishing right ventricular output has been proposed by Cossio & Perianes (70). These observers attempted to achieve this objective by two procedures, ligation of the inferior *vena cava* below the renal veins and tricuspid valvulotomy, the latter being done by a specially devised instrument threaded through the internal jugular vein. After experimental observations with these methods, they were performed on patients with uncontrollable heart failure and pulmonary congestion. Of five patients in whom tricuspid valvulotomy was performed immediate improvement was reported in all but one, although only one patient survived as long as six months. Improvement was also reported following ligation of the *vena cava* but actual data on cases observed were not presented. The practical value of these procedures in mitral stenosis may be seriously questioned, for their lasting effect is obviously doubtful and their risk is admittedly high

The various methods employed in the direct surgical attack upon the stenotic mitral valve include digital dilation, incision or excision and "valvuloplasty" or "commissurotomy" These procedures, with the possible exception of the latter ones, are generally similar to those previously attempted with results that are equally unimpressive. The terms, "valvuloplasty" and "commissurotomy," are employed by Harken (56) and Bailey (58) to designate the operative procedures which they have respectively described and which consist essentially in division of the fused valve leaflets at the commissures with the view of restoring some valvular action with minimal regurgitation. The essential difference between these two procedures seems to be that in the former the commissures are divided by a wedge-shaped resection, whereas in the latter this is done by simple incision. Insufficient time has elapsed to appraise these procedures adequately. Good immediate results have been reported by Bailey in four of seven cases and by Harken in one of two cases, all the others having had fatal termination.

Although at present these procedures appear to offer some promise in selected cases, it would seem that in addition to carrying a considerable risk

they are not essentially constructive procedures. For this reason research along the lines recently reported by Templeton & Gibbon (71) and directed toward reconstruction of cardiac valves under direct vision would seem to provide a more fruitful approach. Similarly the studies of Gibbon and his associates (72, 73), of Bjork (74), and of Jongbloed (75, 76) directed toward development of a method to provide extracorporeal circulation permitting exclusion of the heart and lung during the period required for intracardiac surgery, assume particular significance.

### Myocardial Ischemia

The surgical attack upon the problem of myocardial ischemia has been intensified in recent years, particularly in the experimental laboratory. In general, surgical efforts directed toward alleviation of angina pectoris and coronary sclerosis have taken two lines of approach: (*a*) interruption of the cardiosensory pain-conducting pathways with the possible simultaneous interruption of vasoconstrictor impulses, and (*b*) revascularization procedures designed to provide an additional source of blood to the myocardium.

The former method needs only brief consideration here, for its underlying anatomic and physiologic basis and its technical aspects have been fully discussed in earlier publications (77, 78). Interruption of the cardiosensory pathways is accomplished by chemical (alcohol) block or resection of the upper three or four thoracic sympathetic ganglia, or by posterior rhizotomy at corresponding levels. Choice of the proper surgical procedure depends upon the extent of cardiac involvement and the relative competency of the heart. In patients with sufficient cardiac reserve to tolerate the operation, ganglionectomy appears to be the procedure of choice (78, 79) The value of this method of surgical attack is essentially palliative, for there is no good evidence to show that myocardial function is significantly improved or life appreciably prolonged For this purpose, however, and in light of the predominantly good results (75 to 85 per cent) and low risk (mortality of 10 per cent or less) in properly selected cases (77 to 80) the procedure seems warranted and probably deserves more extensive use.

The other surgical approach to this problem began with the pioneering experimental studies of Beck (81 to 83), who attempted to provide a new blood supply to the heart by grafting tissues onto the myocardium Various tissues have been used as potential sources of new blood supply, both experimentally and clinically, by Beck as well as a number of subsequent investigators These include the pectoral muscle, thoracic wall, pericardium and pericardial fat, omentum, lung, and internal mammary artery (81, 82, 84 to 90). Experimentally, it can be demonstrated that new vascular channels can be produced between the heart and these tissues and that this new blood [illegible]

[illegible] have not been clearly established. More recently, another method proposed

for the relief of angina and improvement of the circulation to the heart consists of ligation of the coronary vein combined with pericoronary neurectomy (91, 92). Clinical evaluation of these methods is difficult, and in view of the high operative mortality [37 8 per cent (82, 83)] and their questionable efficacy, adoption of these surgical procedures has met with considerable reluctance.

The most recent and the most significant development in this field, if for no other reason than as a splendid technical achievement, has been the experimentally successful arterialization of the coronary sinus by Beck (93 to 96) This was accomplished in dogs first by anastomosis with the common carotid artery, and later by a free graft of vein between the aorta and the coronary sinus, the latter having been ligated at an earlier stage This procedure was found to provide effective functional circulation to the heart as determined by critical ligation of a major coronary artery Moreover, it was observed that it was possible by this procedure to deliver too much blood to the heart with fatal effects. According to Beck (96) "significant progress" has not yet been made in the clinical application of this procedure to humans Of five patients operated upon two are living. As Beck himself points out, certain questions concerning this method remain unanswered For example, to what extent is the arterial blood entering the venous system functionally active in providing oxygen-exchange to the tissue? Or how much of this arterial blood entering the coronary sinus by-passes the capillary bed entirely and escapes by communicating channels into the cardiac chambers? Under these circumstances would the effects of an arteriovenous fistula so close to the heart be deleterious? In addition, certain technical problems concerned with preventing thrombosis and maintaining patency apparently still offer some difficulties to be overcome (97 to 99) Finally, the question may be raised concerning the hazards of such a technically difficult procedure in patients with severe myocardial damage (97, 100). Although these and perhaps other questions require further study before the clinical usefulness of the procedure is established, it would seem that this is the most fertile approach to the problem yet developed

## HYPERTENSION

The most significant recent development in the surgical treatment of hypertension is concerned with the efforts to provide a critical evaluation of sympathectomy To be sure, a number of procedures, which vary somewhat in detail, have been proposed with the objective of making the operation more extensive (101 to 105) but it seems doubtful that the beneficial results of these procedures will be significantly greater than those obtained by the more generally employed thoracolumbar operation (106, 107). The more important consideration is proper assessment of surgical therapy.

Complete and precise appraisal of the therapeutic role of sympathectomy in hypertension has been attended with much difficulty. To a great extent this may be explained by the fact that the cause of the disease remains ob-

scure. It may also be explained by variations in the character and prognosis of the disease. Moreover, there seems to be a wide variety of criteria and divergence of methods employed by different observers in assessing the beneficial effects of therapy. Finally, properly controlled study with rigorously comparable series of surgical and nonsurgical cases would be extremely difficult, if not impossible, to make. For these and other reasons the various attempts which have been made to evaluate surgical therapy are all open to question (105, 106, 108 to 117). Perhaps the best efforts of this kind are contained in the recent reports of Evelyn, Alexander & Cooper (118) and Keith, Woolf & Gilchrist (119).

On the basis of these observations as well as accumulated clinical experience, it seems possible now, in spite of the difficulties previously mentioned, to make certain statements concerning the benefits and limitations of sympathectomy in hypertension. (*a*) There is general agreement that fairly complete denervation of the splanchnic bed and lower half of the body is desirable; whether more extensive denervation is necessary and would provide greater benefits is a matter for further study. (*b*) Favorable effects, especially in subjective symptoms, can be obtained in a high proportion of cases, though due consideration must be taken of such factors as age, sex, character of the disease, and extent of the pathologic process. (*c*) The blood pressure can be significantly reduced in about a fifth to a fourth of all cases, even cases of malignant hypertension unresponsive to medical management, but the longer the patients are followed, the less favorable are the results. This is well illustrated by the reported analysis of Evelyn and co-workers (118) in which it was found that the percentage of favorable results two years after sympathectomy was 41, whereas five years after sympathectomy this figure had progressively decreased to 21 (*d*) In general, the best results are obtained in younger patients, preferably those under 45 years of age, with pronounced vasospastic elements and minimal evidences of organic changes. (*e*) The chances of a good result, at least in so far as mortality is concerned, seem to be somewhat better in women than in men. (*f*) Patients with unusually high diastolic pressures do not respond well if serious organic changes have occurred (*g*) In patients with malignant hypertension which is not associated with severe renal or cardiac impairment, sympathectomy may offer the only hope of palliation. (*h*) Patients with the characteristic form of late benign hypertension and with clinical evidence of diffuse arteriolar disease obtain relatively little benefit from the operation. In the more moderate form of benign hypertension without severe associated cardiac or renal impairment, the operation seems to provide some benefits.

Although accumulated experiences and analyses of results have provided certain general ideas concerning selection of cases for operation, there are still, as Palmer (113) emphasizes, "no positive tests or categories by which success or failure may be predicted accurately in an individual patient." A drop in blood pressure to normal or near normal level following bed rest, sedation, spinal anesthesia or other procedures is a favorable but not a

positive sign; it is often observed in patients who subsequently obtain no enduring benefits from operation. According to deTakats & Fowler (108, 109), attempts to distinguish between what is known as neurogenic hypertension, in which sympathectomy might be indicated, and humoral or renal hypertension, in which it would not be, by means of preliminary testing with spinal anesthesia have not been satisfactory.

Finally, certain troublesome and even disabling effects of sympathectomy must be taken into consideration before the operation is performed and must be balanced against the ultimate result. The possibility of their occurrence may be the deciding factor in determining the operability in a given case. They consist essentially, as Palmer (113) has pointed out, in the frequent occurrence of pronounced orthostatic hypotension, neuritis or pain, especially in the back, and often girdle-like, and occasional annoying vasomotor, sudomotor and even visceromotor disturbances which are probably the result of the compensatory or unbalancing effects of the operation. Some of these disturbances may persist for weeks or months, and although most of them disappear in time or can be controlled, they are occasionally severe and disabling.

## Peripheral Vascular Disease

In the field of peripheral vascular disease there has been continued interest in the development of better means of investigation, improved methods of treatment, and more accurate evaluation of therapy. The importance of developing a simple and clinically practical method of measuring peripheral blood flow is generally recognized, for such observations are essential not only in providing better clinical management but also in permitting more accurate objective evaluation of different forms of therapy.

Among the more recent developments directed toward this objective are two methods of study utilizing radioactive substances. In one, blood flow measurement is based upon the "build-up" of radioactive sodium ($Na^{24}$) in the tissues of the extremities following its intravenous injection in the arm (120), whereas in the other it is based on the rate of disappearance of the intramuscularly injected radioactive sodium or its clearance from the tissues (121 to 123). Since several variables, including blood flow, diffusion, and variety of tissues concerned in the measurement are involved in the former method, its use as an accurate means of studying circulatory physiology of the extremities and peripheral vascular disturbance is open to question. For this purpose the second method appears to rest on sounder ground. But here again the rate of diffusion of sodium chloride is an important factor, since the rate of disappearance of the substance deposited in the extravascular spaces must depend not only upon the rate and volume of blood flow in the surrounding tissues but also upon the rate at which the radioactive substance crosses the membranes into the circulating blood and lymph. If it can be assumed that this rate of diffusion is constant under all circumstances of vascular disorders, this method of study can be expected to provide a good indication of the effective circulation of the part. Preliminary observations

by Elkin and his associates (122) and by Kety (121), who devised this method of study, suggest that it does provide a fairly accurate means of determining the clearance of a diffusible ion in tissues, and that this represents a valid quantitative measurement of the regional circulation. It seems, therefore, to offer another valuable aid in the objective evaluation of various forms of therapy in peripheral vascular disturbances and especially in their effect upon the deep circulation of the part.

In the therapy of peripheral vascular disturbances sympathectomy has assumed increasing significance as the most effective means of producing a maximum increase in the blood supply of a diseased part. The rationale of sympathectomy in peripheral vascular disease is the production of vasodilatation by interruption of the vasoconstrictor impulses transmitted over sympathetic pathways to the vascular bed. In the concept of hemodynamics, to which the term hemometakinesia has been applied, a further rational basis for sympathectomy is provided (124, 125). This concept is derived *from certain observations concerning the physiology of the circulation which* establish the presence of spontaneous and even rhythmic fluctuations in the volume of organs primarily attributable to changes in the volume of blood within the part. These fluctuations of the blood volume in different parts of the body can occur without any alteration in the total blood volume by an adjustment of the vascular bed which permits simultaneously an increase in the volume of blood (vasodilatation) of one part of the body and a corresponding decrease elsewhere (vasoconstriction). This, in effect, constitutes a compensatory mechanism permitting the "borrowing and lending" of blood by the various tissues to meet variations in requirements. It is indicative of a well regulated mechanism designed to permit the body to utilize its limited total blood volume in the most efficient manner In this mechanism of control and regulation of the peripheral vascular bed, which provide adjustments in the volume of blood in the part, the sympathetic nervous system plays an important role. Interruption of the sympathetic pathways, to the part removes the vasoconstrictor factor in this mechanism and through the resultant maximum vasodilatation in the vascular bed provides an increase in the circulation of the part

In the treatment of peripheral vascular disease, other means of producing such vasodilatation by the use of various vasodilator agents have long been attempted with little success More recently with the development of more [illegible]

(126 to 129) have reported highly favorable results following the use of these agents in all types of peripheral vascular disturbances Other investigators (124, 125, 130 to 132), however, have not been able to confirm these observations. Under controlled atmospheric conditions and using thermometric and plethysmographic methods of determining blood flow, Ray, Burch & DeBakey (124) observed that none of these vasodilator agents

could consistently produce, in a local peripheral part, vasodilatation equal either in degree or duration to that produced by sympathetic denervation of the part.

The indications and the value of sympathectomy in various forms of peripheral vascular disease have been recently reviewed by a number of observers (133 to 136). Although it is generally agreed that sympathectomy may be the most effective means of improving the circulation in many of these disturbances, it is also recognized that depending upon the type and extent of the disease, as well as on other factors, considerable variation exist in its efficacy. Much attention has been recently devoted to the factors which may alter or modify the enduring effectiveness of sympathectomy in peripheral vascular disturbances, particularly the phenomenon of return of vasomotor activity after sympathectomy. Extensive considerations of this problem with a critical evaluation of the factors involved have been presented in several recent reviews (107, 133, 134, 136 to 138). Among the most important factors concerned with this problem are local vascular faults, variable pathologic processes, increased responsiveness of denervated smooth muscles to circulating vasoconstrictor substances, regeneration or incomplete interruption of sympathetic pathways, recovery of intrinsic vascular tone, abolition of vasodilator influences, reorganization of neurogenic vasoconstrictor function within the sympathetic system, and residual sympathetic pathways (133). On the basis of present knowledge it is difficult to evaluate the relative importance of the role played by each of these factors in modifying or limiting the enduring effectiveness of sympathectomy. It is possible that depending upon the nature of the disturbance and the type of procedure performed each one of them singly or in combinations may be operative and further studies are needed to clarify the problem. As emphasized previously (133), however, although it is important to acknowledge and appreciate the significance of possible limiting factors of sympathectomy, it is equally important to recognize that they do not necessarily contraindicate the procedure or even greatly restrict its application. They are important in the critical evaluation of the operation, and they constitute special problems which still require solution.

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# DISEASES OF THE KIDNEYS[1]

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Classification of the diseases first described and grouped together by Richard Bright continues to be unsatisfactory and unsettled Nearly every author uses a personal arrangement of these conditions, but in general there is a tendency to accept some modification of the threefold division by Volhard and Fahr into the nephritides, nephroses and nephroscleroses. No attempt has been made to agree upon a uniform system and little may be expected in this direction until the confusion regarding pathogenesis is cleared. This review deals with recent contributions in the study of bilateral nonsuppurative inflammatory (nephritides) and degenerative (nephroses) renal diseases The renal disorders associated with essential hypertension (nephroscleroses) and the problems of arterial hypertension have been omitted from the discussion to be covered elsewhere in this volume.

A number of monographs on Bright's diseases have appeared in the past three years. The pathology of these conditions has been reviewed and extensive additional material presented by Bell (1). Allen (2) has published an atlas of the histopathology of renal disease under the auspices of the American Registry of Pathology This work may be used in conjunction with slide sets on loan from the Army Institute of Pathology Unfortunately the book is marred by poor printing and an inadequate text. General reviews of renal function with special reference to abnormal states have been written by Hamberger & Ryckewaert (3) and by Spuhler (4). The clinical manifestations are considered at length by Addis (5) and Christian (6).

## The Nephritides

*Diffuse glomerulonephritis.*—It is becoming increasingly certain that the predominantly glomerular lesions of diffuse glomerulonephritis are the result of a selectively specific tissue reaction. Thus, Simonds *et al* (7) failed to produce lesions resembling those of glomerulonephritis with various nonspecific tissue poisons, even when they were protein-bound or colloidal in nature so that capillary damage might have been expected to predominate in the glomeruli as the result of concentration of the damaging agent through loss of water by filtration. In these experiments, rattlesnake and moccasin venoms, and diphtheria, streptococcal and staphylococcal toxins were employed. All except streptococcal toxin caused as much or nearly as much tubular injury as glomerular. Streptococcal toxin had little effect of any kind.

[1] This review covers the literature for the years 1946 to 1948 inclusive, and the early months of 1949. It is necessarily selective, but every effort has been made to include references to all significant material published during this period.

Nonetheless, there is little doubt that an excellent correlation exists between the appearance of a streptococcal infection and the onset of acute diffuse glomerulonephritis.

The Caveltis (8, 9) have recently shown that autoantibodies to kidney may appear in the blood of rats or rabbits following injection with emulsions of homologous kidney mixed with ether-killed streptococci. A significant number of these animals (10, 11) developed acute diffuse glomerulonephritis, which progressed in some instances to the chronic stage, and finally death in uremia. Proliferative or obliterative lesions were found in most glomeruli. Moreover, autogenous tissue antigens (including kidney) demonstrable with appropriate antisera appeared in the blood of rats infected with Group A beta hemolytic streptococci (12) These experiments have not been confirmed, and Humphrey (13) has been unable to repeat them.

Proof that autoantigen and autoantibody production occurs similarly in human nephritis requires the demonstration of antibodies to human kidney in the blood of patients with the disease, or of circulating autogenous renal antigen during streptococcal infection. Lange *et al.* (14), using the collodion particle technique employed by the Caveltis, have found high titers of antibodies to human kidney in 68 to 78 per cent of examinations of blood from 23 cases of acute and chronic glomerulonephritis In 68 control subjects only 19 per cent of examinations were positive. This is somewhat puzzling, since antibodies might be expected to appear but briefly in the blood early in the course of the disease and then disappear completely as the result of binding by the renal antigen. The collodion particle technique is difficult and erratic; further work and confirmation is needed before Lange's findings are generally accepted. The fact that the serum complement titer may and often does fall precipitously with the onset of acute nephritis has been confirmed by Fischel (15) and Reader (16), and appears to implicate an antibody-antigen reaction in causation.

Seegal & Loeb (17) have produced typical glomerulonephritis in rats following injection of antirat-placenta rabbit serum. In this case antibodies to one tissue act upon another perhaps because of an underlying similarity of antigenic proteins. Likewise glomerulonephritis appearing in rats one week after massive injection of bovine globulin [Hawn & Janeway (18) and More & Waugh (19)] may arise in connection with the demonstrable production of antibodies to globulin, and even nephrotoxic serum nephritis in rats appears to depend upon the formation of antibodies to foreign serum protein (20) Rigdon *et al.* (21) and Rytand (22) suggest that instances of glomerulonephritis appearing subsequent to or during episodes of sulfonamide reaction and poison oak dermatitis respectively may result from such a nonspecific sensitization.

Doan and his co-workers (23) have observed acute diffuse glomerulonephritis in five monkeys receiving streptococcus hemolyticus and influenza virus in sequence by intranasal inoculation, followed by reinoculation or spontaneous reappearance of the streptococci. Whether the viral infection

altered streptococcal activity in any manner is unknown, but evidence that it depressed the humoral and cellular responses to infection is particularly interesting in connection with the view that glomerulonephritis may arise from some abnormality of immune mechanisms.

Pressman (24) has brought forward evidence that the site of the antibody-

[illegible]

autographs. Iodinized globulin in normal sera did not accumulate in the

[illegible]

but not by adsorption with other portions of rat kidney, indicating that the "antigen essential for the production of anti-kidney sera was of glomerular origin."

Although glomerulonephritis has been studied intensively for more than a century, its natural history remains uncertain and obscure. The orderly progression of changes from acute to chronic stage, described by Addis (5) and others, is often seen, but frequently the nephrotic phase or the terminal form of the disease may appear independently without any evidence of a preceding illness. In these instances it is generally believed that the initial episode has been so minor or fleeting that it has passed unobserved. This view has been challenged by Ellis (26), who recognizes two separate forms, which he calls Type I and Type II. Type I is characterized by onset with typical acute diffuse glomerulonephritis, it is usually benign but may run a rapidly progressive course with persistent edema and hypertension to end in uremia. In others it may go on to chronicity with slow deterioration of renal function and the development of hypertension Type II includes all those cases of insidious onset which pursue a prolonged course characterized by more or less persistent edema and proteinuria, often ending as Type I. A clinico-pathological survey of 188 cases of all varieties of renal disease was made by Davson & Platt (27) to assess the validity of this classification. Forty-five cases appeared to satisfy Ellis' criteria for diagnosis as Type I or Type II nephritis, and the authors conclude that his classification is practical and helpful, though they reserve judgment as to whether the two types are variations of the same disease They observed no reliable instance of a nephrotic phase following the acute episode, preceding the development of the terminal stage, and suggest that, while it may occur, such a course is uncommon. Nonetheless, Bloom & Seegal (28) found that 54 per cent of a group of 54 patients dying in uremia due to chronic diffuse glomerulonephritis exhibited signs of the nephrotic phase at some time in the course They found no evidence of repeated episodes of nephrotic syndrome with complete remissions as in a case observed by Derow (29)

The factors determining chronicity are entirely obscure. Longcope (30)

believes that repeated episodes of streptococcal infection are necessary, whereas Seegal (31) stresses the facts that nephrotoxic nephritis in rats may pass from the acute to chronic stage after a single injection of nephrotoxic serum and that chronic nephritis in man may progress without evidence of exacerbations of the acute process. The latter viewpoint seems to be supported also by the behavior of the disease after the initial episode of acute diffuse glomerulonephritis. Recent reviews by Ramberg (32), Rudebeck (33), and Burke & Ross (34) survey the outlook in an aggregate of 521 cases of acute diffuse glomerulonephritis. In their cases the development of the chronic stage appeared to depend largely upon the severity of the initial renal lesion, whereas repeated attacks of acute nephritis could not be proved to have prognostic significance (33). Most instances of chronic diffuse glomerulonephritis come to the attention of the physician without a story of earlier episodes of acute diffuse glomerulonephritis This may mean that the disease is exceedingly common in the population at large, the milder undetected cases comprising an overwhelming proportion of the total, so that a disproportionate representation of such cases appears among the group of chronic nephritics. Or it is possible that other as yet undetermined factors are more important in deciding outcome than the apparent severity of the initial attack

On the whole, the figures of the various authors concur in showing a much better prognosis in children than in adults. According to Rudebeck (33) 86.3 per cent of 73 patients between 10 and 19 years of age recovered completely, whereas but 51 4 per cent of 37 patients between 40 and 49 recovered Similarly Ramberg (32) found that 70 per cent of children and only 47 per cent of adults above 25 years of age with the disease were cured. It is agreed that the initial episode occurs usually at an early age and affects males somewhat more frequently than females In all series, upper respiratory diseases usually preceded the onset and when diligently sought the streptococcus appeared to be implicated in more than half. From time to time the incidence of acute nephritis takes an unaccountable upturn. Thus, so-called "epidemics" have been recently reported in England (35) and the Netherlands (36, 37) Fleming (35) reports 159 cases admitted to a single hospital in a small industrial community in Renfrewshire, England, during the years 1945 and 1946. Most were adults, but this circumstance is possibly attributable to the nature of the receiving service and to failure of admission of milder cases among children, since it appeared that for every case brought to the hospital there were five treated at home The upswing in Holland developed during 1945 and was commented upon by observers in Zutphen (36) and Amsterdam (37).

The pathology of diffuse glomerulonephritis has been reviewed *in extenso* by Bell (1). Glomerular lesions characterized by increased cellularity, infiltration of the axial space with leucocytes (38), thickening of the basement membrane, and adhesions between the tuft and capsule are prominent in the early phase. Later, hyalinization and obliteration take place, there is a more

serious disturbance of the tubular and interstitial tissue, and the structure of the organ as a whole is profoundly altered. Mulmed and his co-workers (39) comment upon the paucity of change found in a patient during the latent stage, indicating that severe dysfunction is consistent with relatively little structural abnormality.

The development of refined tools for the study of renal function has permitted a more exact analysis of the pathologic renal physiology of diffuse glomerulonephritis. Earle and his co-workers' (40) study of the changes in glomerular filtration rate, effective renal blood flow, and maximal tubular transfer rates has been repeatedly confirmed (3, 41 to 44). In the acute stage, glomerular filtration appears to be preferentially affected, renal blood flow changing less markedly. Indeed, catheterization studies (31, 45) have revealed reduction in sodium *p*-aminohippurate (PAH) extraction indicating that measurement of blood flow by clearance methods may yield falsely low values. Thus, the renal blood flow may be greatly increased in acute nephritis even though filtration is diminished Black (44) has suggested that marked afferent vasoconstriction plays an important role in decreasing filtration by lowering filtration pressure, but this view is difficult to reconcile with evidence of actual hyperemia. Undoubtedly, intense and widespread intrarenal arteriolar constriction contributes in certain cases, but even in these the factor of glomerular damage is important. The filtration surface is reduced in area by capillary occlusion and by exudative proliferation with ultimate loss of glomeruli. The reduction in tubular transport maxima (Tm) and in PAH extraction by the kidney apparently indicates a serious disturbance of tubular tissue which is not evident at first to the pathologist These associated defects could arise as the result of shunting of blood away from functioning tissue, perhaps on the basis of some such intrarenal circulatory change as observed by Trueta *et al* (46) in animals subjected to trauma or sciatic stimulation. In keeping with this view is Cargill & Hickam's (47) observation that renal oxygen arteriovenous difference decreases during acute and subacute glomerulonephritis. This change might also occur, however, as a result of reduced renal oxygen consumption following loss of tubular tissue. Later, as nephrons are destroyed and partially replaced by fibrous tissue the architecture of the kidney is profoundly altered and function correspondingly impaired. Distortion and contraction of the renal vasculature appears to follow this change in structure with progressive diminution in blood flow, though the blood flow per unit of functioning tissue may be increased.

Glomerular filtration improves after recovery from the acute episode, and may be within normal limits early in the course of chronic nephritis during the nephrotic phase (48). Marked loss of plasma protein in the urine at this stage, however, bespeaks a serious disturbance in glomerular capillary permeability, even though structural change is not demonstrable. Ultimately, as glomeruli and tubules disappear, tubular activity diminishes, filtration decreases, and renal function becomes totally disorganized These serious functional disturbances in acute and chronic glomerulonephritis interfere

with renal regulation of body water composition and volume. Almost any conceivable disorder of the chemical structure of body fluids may develop at some time. In each, specific derangements of glomerular and tubular function may be discerned, but it is not always possible to attribute these dysfunctions exclusively to specific anatomic lesions of glomerulonephritis.

Coincidental anemia, dehydration, blood loss, arterial hypertension, heart failure, wasting, and other extrarenal disorders may influence renal function detrimentally. Collateral endocrine and metabolic disturbances can also cause trouble Knowlton and her co-workers (49) have recently shown that desoxycorticosterone acetate accelerates the course of nephrotoxic nephritis in rats. Parathyroid hyperplasia frequently occurs in chronic uremia and may be responsible for abnormal bone growth and development. With all these elements to be considered, it is obviously impossible to set out a definitive therapeutic program. Attempts to simplify the problems of management tend to be misleading and confusing. These problems will be considered below.

*Cardiac decompensation occurs frequently* in the course of glomerulonephritis. In the chronic stage it is usually attributable to the development of hypertension or to the appearance of arteriosclerotic vascular disease The immediate causes are much less apparent in the acute episode. Here it may occur with distressing frequency. Burke & Ross (34) noted signs of congestive heart failure in 35 of 62 patients (56.5%) with acute nephritis, whereas Rudebeck (33) encountered failure in only 84 of 318 patients (26.4%). This disparity is familiar in other studies, a wide range of incidence being reported, depending in part on the nature of the clinical material, on a special interest in cardiac involvement, on the criteria employed, and on the vagaries of the disease Though hypertension is apparently the underlying pathogenic factor in many cases, a good general correlation between cardiac enlargement and hypertension is lacking Dean (50) has shown that this may be true in chronic diffuse glomerulonephritis as well There is some evidence that renal retention of water may be concerned in some manner. Both Cardozo (51) and MacArthur (52) have found evidence of hemodilution in the acute stage and a sharp drop in plasma volume during diuresis, suggesting that augmented plasma volume may have played a role in precipitating heart failure. However, MacArthur found that the plasma volume tended to return to the levels obtaining during edema as recovery proceeded It seems likely that congestive heart failure is rarely, if ever, induced by augmentation of plasma volume alone, but requires an underlying disorder of the myocardium.

Electrocardiographic changes have been shown to occur even more frequently in acute nephritis than overt signs of heart failure (53, 54, 55). LaDue & Ashman (55) have found a rightward deviation of the ventricular gradient in most cases, often in association with low or negative $T_1$, a reciprocal increase in the voltage of $T_3$, and prolonged Q-T interval. A similar change in gradient occurs as the result of ischemia of the left ventricle. A widespread serous effusion into the interstitial tissues of the myocardium,

thrusting muscle bundles apart, was found by Gore & Saphir (56) in 16 of 160 cases of acute and subacute glomerulonephritis. Previous investigators have failed to find such a high incidence of myocardial pathology. The question of the pathogenesis of heart failure in glomerulonephritis remains obscure, therefore, and its answer must await further study.

Neurologic disorders arising as part of the course of glomerulonephritis are now generally believed to be caused by coincident hypertensive vascular disease. Convulsions and other symptoms of central nervous system involvement may occur during acute nephritis. Rudebeck (33) found only eight instances among 356 cases. There is some question regarding the underlying cause of such encephalopathies; Rubin (57) considers cerebral ischemia secondary to marked vasospasm to be the chief factor, whereas Adams (58) believes cerebral edema is at fault.

Anemia occurs frequently in acute nephritis and in the terminal stage, less commonly in the latent or nephrotic stage. Emerson (59) obtained extensive hematologic data in a 27-year-old patient with acute nephritis over a 50 day period during which anemia rapidly developed. Using the technique of differential agglutination following administration of group O blood cells to a group A recipient, he found that increased blood destruction occurred, involving both donor and recipient cells. However, a reticulocytosis was induced without much improvement of the anemia, suggesting that impaired blood formation and augmented blood destruction both played a role. Similar studies of the anemia of chronic nephritis have revealed increased hemolytic activity as well as depression of erythropoiesis, the donor cells disappearing from the blood at 1.5 to 3 times the normal rate. Since anemia has been shown (60) to interfere with renal function by inducing intrarenal vasoconstriction it has seemed likely that correction of anemia might serve to correct in part at least the associated renal insufficiency. Salvesen (61) and Emerson (62) have failed to find any evidence of functional improvement following massive transfusion in 14 cases of uremia due to chronic Bright's disease. Indeed, in two cases of Salvesen, aggravation of symptoms followed transfusion.

Treatment of glomerulonephritis is entirely symptomatic, as one would expect in view of the inadequate information available on causation. Chemotherapeutic agents appear to be useful only insofar as they control the initiating streptococcal infection or secondary infections of other kinds. Sen (63) treated acute nephritis with penicillin (total dosage 192,000 to 640,000 Units) in 12 children, with what he believed to be encouraging results. One child died; the others recovered 4 to 37 days after onset and 3 to 7 days after treatment was begun. However, in view of the vagaries of the course and the usual range observed in patients recovering spontaneously, these results cannot be construed as hopeful. Likewise, Fleming (35) failed to present convincing evidence that penicillin altered the course in 50 ad[illegible]

pressure in acute nephritis (heart failure and encephalopathy) by continuous caudal analgesia. In six individuals Hughes *et al* (65) observed a reduction in blood pressure with some amelioration of related symptomatology but their data are insufficient to show a definitely beneficial effect. They do not recommend the use of this procedure until other measures have failed.

Dietary restriction of protein is urged by Addis (5) and his associates (66) through most of the course of glomerulonephritis in the belief that renal work is largely a function of nitrogen excretion. Addis (5) has recently published a full-scale defense of this thesis. However, the numerous nonexcretory activities of tubular cells appear to account for an overwhelming proportion of energy development and utilization in the kidney. It seems reasonable to restrict protein food during acidosis, when various nonmetabolizable organic and inorganic anions may accumulate in the blood and intensify the prevailing electrolyte imbalances. Rudebeck (33) could find no evidence that different dietary programs altered the course or outcome in any way among his group of patients with acute nephritis. Indeed, it appeared that prognosis improved slightly when the dietary restrictions were eliminated. Mortensen (67) employed a high protein diet without evidence of ill-effect.

Activity is usually strictly limited in the acute stage until azotemia, edema, hematuria, and proteinuria have cleared or stabilized. However, critical studies of the value of protracted bed-rest are lacking and no evidence is available that it is of great benefit (33). Persike & Lippman (68) have emphasized the importance of psychiatric management. Reassurance of parents is often as necessary as reassurance of patients, since parental anxieties may result in serious emotional disturbances in sick children. Tonsillectomy to eradicate a possible focus of infection has been repeatedly assailed (33, 69) and it now seems reasonable to limit the operation to those patients in whom local pathology warrants it Successful pregnancy without further injury to the kidney is possible even in advanced chronic diffuse glomerulonephritis of many years duration (70, 71)

*Focal glomerulonephritis*—Whether the appearance of hematuria and moderate proteinuria at the height of a febrile illness in the absence of renal insufficiency or hypertension should be interpreted as a form of acute diffuse glomerulonephritis remains controversial. In some instances of this kind progression into chronic nephritis has been observed, but on the whole the prognosis is much better than for the typical forms of acute diffuse glomerulonephritis (33) The "pyrogenic reaction" (typhoid vaccine) may evoke hematuria in normal individuals, and it gives rise to renal hemodynamic changes resembling those observed in some instances of acute nephritis (72). Hence, the overlap between the diffuse and focal disorders may obscure an essential difference

*The visceral angiitides*—Periarteritis nodosa gives rise to inflammatory [illegible] the kidney that affect the glomeruli as well as larger vessels

a form of glomerulitis, but tubular damage may ultimately develop. Considerable interest has been shown in periarteritis nodosa during recent years because it has been produced experimentally (74, 75, 76) and because certain evidence indicates that it may be a manifestation of hypersensitivity to a variety of therapeutic agents including sulfonamides (74, 77). An interesting symposium covering various aspects of the disease has appeared in the Proceedings of the Staff Meetings of the Mayo Clinic (78), and other reviews (79, 80, 81) have recently appeared. The pathologic changes in the kidney include the development of widespread arteriolar sclerosis, focal or diffuse glomerulonephritis and multiple infarction (78, 82). Several instances of massive perirenal hemorrhage have been reported (78, 83, 84). Flank pain, spasm of the upper third of the ureters, and other manifestations of urinary tract involvement may confuse the clinical picture (85, 86).

Lupus erythematosus is associated in most cases with widespread renal lesions ranging from thickening of the basement membrane of scattered glomerular capillaries with necrosis of the capillary wall ("wire loop" lesions) to diffuse glomerulonephritis or focal glomerulitis. Out of 21 cases, Bell (1) found one or more of these lesions in 14. Occasionally the disorder is manifested clinically as typical acute diffuse glomerulonephritis. It is claimed that the characteristic skin lesions may be insignificant or absent. Renal insufficiency and hypertension may occur, and Brenner *et al.* (87) have recently described an instance of the "nephrotic syndrome" in a young woman without skin manifestations who died in uremia and congestive heart failure on the basis of renal and cardiac pathology attributable to lupus erythematosus.

*Pyelonephritis*.—Raaschou (88) has written an important and interesting monograph on his studies of 202 cases of chronic pyelonephritis. He claims that this disease accounts for 5.6 per cent of all deaths and for 57.8 per cent of deaths in uremia at the Kommunehospital in Copenhagen. A third of his cases occurred in the absence of overt urinary tract pathology However, Bell (1) found but 808 cases among 32,360 necropsies (2 5 per cent) and but 8 6 per cent of these did not have an associated hydronephrosis. It must be admitted that diagnosis is often very difficult since all progressive and extensively destructive renal diseases tend to produce more or less similar pathologic changes in the end stage

Pyelonephritis apparently begins with direct bacterial invasion and inflammation of the urinary tract, collecting ducts and renal tubules Glomerular involvement follows. There is usually evidence of marked interstitial inflammation which may be so intense that multiple focal abscess formation occurs. Ultimately, loss of nephrons and proliferation of interstitial connective tissue results in scarred contracted kidneys resembling those of chronic diffuse glomerulonephritis.

Raaschou has measured inulin and diodrast clearances and the rate of maximal tubular excretion of diodrast (Tm) in 32 patients. These values fell in a parallel manner with progression, but ultimately the diodrast clearance and diodrast Tm were affected more than the inulin clearance,

presumably because tubular injury was predominant. In a few cases the functional changes and clinical pattern suggested that acute diffuse glomerulonephritis and pyelonephritis might occur simultaneously. Much more work of this kind is necessary to clarify the functional derangements in pyelonephritis and to determine its role in producing such clinical states as "Fanconi's syndrome" and "Milkman's syndrome" in which tubular dysfunction is prominent

Urinary tract disease is usually present but occasionally no obvious predisposing factors can be detected. Attention has recently been called to the frequency of pyelonephritis among diabetics (89). Robbins & Tucker (89) found that 6.7 per cent of diabetic patients on whom necropsies were performed at the Mallory Institute died in uremia during an episode of acute pyelonephritis. Most of these patients were found to have necrotizing papillitis of the renal pyramids In 26 cases studied by Robbins, Mallory & Kinney (90) this lesion was characterized by a "pale yellow-white infarct-like necrosis of the papillae, bordered above by a green-to-red zone of inflammatory reaction." Edmondson, Martin & Evans (91) found papillary necrosis in 50 of 32,000 consecutive necropsies, of which 29 were diabetics (out of a total of 859 diabetics). In their series it occurred most frequently among diabetic women over 40 years of age. In nondiabetics it appeared predominantly in males, usually as a complication of disease of the prostate.

## The Nephroses

Nephrosis is a portmanteau word covering a large group of renal disorders which are primarily characterized by tubular pathology. Degenerative and necrotizing lesions are incorporated together under this head On the whole, the nephroses may be broken down into two subsidiary groups which differ markedly. The proteinuric nephroses are manifested clinically by the "nephrotic syndrome" or by proteinuria alone Tubular lesions here appear to be secondary to increased filtration of plasma proteins A glomerular defect which may not be detectable anatomically apparently permits plasma proteins to escape into the glomerular filtrate. If the cause can be found and removed, complete recovery usually follows. Prolonged and massive filtration *of protein may ultimately cause irreversible tubular injury.* The necrotizing nephroses are much more destructive. Various poisons (such as heavy metals, carbon tetrachloride, sulfonamides, and many others), shock, and intravascular hemolysis are among the more important causes An effort has been made by pathologists to classify the necrotizing nephroses according to the site of major tubular pathology. Heavy metals affect the proximal convoluted tubules preponderantly, causing what may be referred to, therefore, as "upper nephron nephrosis." Severe shock, on the other hand, may give rise to destructive lesions in the distal segment or "lower nephron nephrosis" (92). This term has caught on very rapidly in this country since its introduction by Lucké, and it has served a useful purpose in providing a single term for the group of confusing renal disorders which result from intra-

vascular hemolysis, circulating "heme" pigment, and/or shock. However, it has also caused some confusion. First, most of the conditions to which it is applied may present some upper nephron pathology. Lucké included certain disorders in which the lesion lies predominantly in the proximal segment. Hence there is a growing tendency to apply the term as a general expression embracing all types of necrotizing nephrosis. Second, a concrete term of this type applied to such a complicated group of disorders tends to obscure the fundamental confusion regarding etiology and implies that we are dealing with one rather than several conditions.

*Proteinuric nephroses.*—Proteinuria of varying intensity characterizes all these disorders. This abnormality in turn may give rise to the "nephrotic syndrome" consisting of hypoalbuminemia, hypercholesterolemia, and generalized edema (93). On the basis of present knowledge, it appears to be a unique and discrete entity in its own right, having certain uniform characters regardless of underlying cause. The chief differences of opinion concern the source of protein in the urine, the causes of edema and the significance of lipidemia.

Studies of the chemical and physical character of plasma and urinary proteins in nephrotic children indicate that albumin is the chief protein lost from the plasma and the most important constituent of the urinary proteins (94, 95, 96). According to Albanese *et al.* (97), the amino acid constitution of the urine albumin (obtained by salting-out methods) differs strikingly from that of plasma albumin, and they suggest that urinary protein may be synthesized in the tubules and excreted. However, there are reasons to believe that data of this kind may be defective, because pure albumin cannot be obtained by precipitation methods (98). Hypoproteinemia is therefore generally believed to result from protein loss in the urine. Defective protein manufacture by the liver has been considered a possible contributing cause. However, Kunkel & Ward (99) have found that hepatic synthesis of plasma esterase, a protein, is normal in patients with the nephrotic syndrome, although it may be accelerated during remissions or following albumin therapy. Other tests of liver function are normal.

There is now good reason to believe that a very small proportion of plasma protein is normally filtered at the glomerulus and reabsorbed by a limited tubular transfer system (100, 101, 102). Intravenous administration of massive doses of plasma proteins to experimental animals results in proteinuria, apparently because the amount of protein filtered is increased and reabsorptive mechanisms overtaxed. Tubular lesions resembling those of nephrosis (103) may be produced in this way. Gelatine produces a similar effect (103, 104).

These findings suggest that the tubular pathology of the proteinuric nephroses may be secondary to reabsorption of large quantities of protein from the glomerular filtrate. It is possible that inefficient reabsorption may account in part for proteinuria, but the mass of protein appearing in the urine is often too large to be explained entirely on this basis, and a defect

in the glomerular membrane permitting filtration of much more protein than normal must be postulated.

Edema formation appears to be the result of a combination of movement of water from the plasma into the tissues and of retention of water and salt in the body by the kidney (48). Rapid escape of injected albumin concentrates and of protein-bound dyes from the circulation suggest that altered capillary permeability (105, 106) as well as reduced plasma oncotic pressure is responsible for the loss of fluid from the plasma. In consequence hypovolemia develops (107) and probably plays a role in provoking renal retention of sodium and water (108 to 111). Administration of albumin concentrates with re-expansion of plasma volume results in augmentation of glomerular filtration and renal blood flow (48, 107, 112, 113). Cargill (113) has noted a fall in renal extraction of PAH and suggests that this may indicate derangement of tubular function or the operation of shunts. However, he gave albumin very rapidly, and it is possible that the changes observed may have been the result of technical difficulty in preventing mixture of renal venous blood with blood from the inferior vena cava. Fox and his co-workers (114) suggest that sodium may be retained because a sodium deficit has occurred, and recommend the use of sodium salts in treatment. Diuresis was induced in 14 children after administration of sufficient sodium lactate or sodium and potassium acetate to raise the blood level to 140 m.eq. of sodium or over. Corson & O'Leary (115) obtained a similar diuresis in animals, made hypoproteinemic and edematous by plasmaphoresis, following the use of sodium succinate and fumarate. However, other workers (116, 117) have failed to find a rise in serum sodium preceding the onset of spontaneous diuresis in nephrotics, though an increased water output seems to precede augmented sodium excretion

The cause of hypercholesterolemia and lipemia remains obscure. Undoubtedly renal dysfunction *per se* plays a role, since renal insufficiency produced by various means has been shown to give rise to lipemia (118, 119). Simultaneous liver injury seems to prevent this response (120). Ahrens & Kunkel (121) find that the ratio of serum phospholipids to total serum lipids is low in nephrotics, suggesting that the serum is milky owing to a low proportion of hydrophilic lipids rather than to an abolute increase in neutral fat, as is commonly believed. Enzymatic hydrolysis of phospholipids in normal or nonmilky high-lipid sera resulted in the production of a lipemia resembling that of nephrosis. They conclude therefore that "phospholipids exert an appreciable solubilizing effect upon hydrophobic lipids" which is lacking in nephrosis.

Since the nephrotic syndrome often clears spontaneously it has been difficult to assess the numerous therapeutic measures It has seemed reasonable to believe that replacement of the protein lost in the urine should have a beneficial effect, but after initial enthusiasm the use of newly developed salt-poor human albumin concentrates has proved somewhat disappointing (95, 96, 122 to 126). A large percentage of the injected albumin is lost in

the urine, diuresis does not follow its use in some cases and may be limited or transient in others, and cardiac enlargement with an elevation of arterial pressure may preclude its use. Other diuretic agents, including gelatine (123, 125), acacia (127) and globin (128), have been recommended.

Perhaps the simplest variety of proteinuric nephroses is exemplified by benign proteinuria and the so-called larval nephroses, which appear during febrile illnesses. It seems reasonable to believe on the basis of information available today that proteinuria during fever, congestive heart failure, and various infectious diseases is linked to intrarenal circulatory disturbances that alter glomerular capillary permeability. Orthostatic proteinuria is likewise probably attributable to local circulatory changes Bull (129) has recently advanced the thesis that this disorder results from interference with the outflow of blood from the inferior vena cava in the upright, lordotic position. He failed to find any correlation with body build. Protein was detected in the urine coming from both kidneys, and bilateral proteinuria could be produced by upward rotation of the liver, possibly because the inferior vena cava was compressed between the spine and the posterior surface of the liver, with elevation of renal venous pressure. However, increased intra-abdominal pressure alone may cause proteinuria in association with a reduction in both renal blood flow and glomerular filtration rate (130). Bull did not test the relationship between increments of intra-abdominal pressure and the appearance of proteinuria in his patients

Lipoid nephrosis is chiefly a problem in childhood. It is characterized clinically by the nephrotic syndrome and pathologically by the absence of renal pathology. The question of its relation to diffuse glomerulonephritis remains unsettled, although there is a tendency to consider it a discrete entity (131, 132). In adults the nephrotic syndrome is usually a manifestation of chronic diffuse glomerulonephritis (133). The ultimate outlook in children is favorable, but lowered resistance and various local changes are conducive to a high incidence of secondary infections. With the development of effective chemotherapeutic agents, the prognosis has improved greatly, the fatality rate having dropped from about 30 per cent to 15 or 20 per cent in the last decade Dietary measures do not seem to be particularly effective. Some clinicians (132) continue to use thyroid extract with benefit Much attention has recently been paid to the striking remission which often follows measles and other virus diseases Several groups (134 to 137) are now engaged in studies of this effect in children deliberately infected with measles virus The phenomenon indicates the essential reversibility of the underlying lesion, and it may provide a means by which more effective and perhaps even specific therapy may be achieved Janeway and his co-workers (137) note that "a sharp decrease in proteinuria precedes diuresis and fails to occur in those who do not diurese, and serum proteins do not rise significantly until diuresis is occurring," indicating "an effect of measles on the kidney rather than on protein metabolism in general. This may be taken as one more piece of evidence in favor of the concept that lipoid nephrosis primarily is a disease

of the kidney rather than an obscure disorder of protein metabolism." Albumin therapy is widely used with variable results.

Intercapillary glomerulosclerosis has been recognized with increasing frequency since the first description of the glomerular lesions by Kimmelstiel & Wilson (138) in 1936. Whether the hyaline laminated nodular masses between glomerular lobules are specifically related to diabetes mellitus or arise as part of the widespread arterial and arteriolar degenerative disease so common in diabetes remains disputed (139). Certainly the lesions are much more prominent among diabetic patients and they appear in animals with diabetes mellitus induced by pituitary extract (140) or alloxan (141). Clinically, the nephrotic syndrome, renal insufficiency, and hypertension may occur simultaneously, but this picture is by no means pathognomonic since it may occur in other renal diseases (142, 143). As aids in diagnosis, Henderson *et al.* (144) and others (145) have stressed the frequency with which combined hypertensive and diabetic retinopathy occur in this disorder, and Rifkin *et al.* (145) have regularly found doubly refractile fatty cells and casts in the urinary sediment. It is impossible to say whether therapeutic control of diabetes modifies the course in any way, though it is claimed (146) that patients with severe diabetes never escape vascular complications when the disease is poorly controlled.

Renal amyloidosis is nearly always secondary to disease elsewhere in the body though occasionally it occurs in primary amyloidosis (147). The Congo red test has been a mainstay in diagnosis Selikoff (148) has found that complete or almost complete absorption of the dye from the blood on at least two different occasions is necessary to make a definitive diagnosis of amyloidosis. Unfortunately, several severe reactions and at least two fatalities have been reported (149) following the use of Congo red Selikoff & Robitzek (150) find that gingival biopsy may be helpful in diagnosis Of 18 cases with a reasonably certain diagnosis on clinical grounds, 14 were found to have amyloid material about vessels in a biopsy (about 2 by 5 mm in size) taken from the gum and mucobuccal fold.

Thomas & Schur (151) have observed 10 instances of nephrosis as a manifestation of secondary syphilis. Proteinuria, oliguria, and occasionally edema develop in association with the skin rash. Penicillin or arsenotherapy may have a strikingly beneficial effect (152, 153)

Heavy Bence-Jones proteinuria during multiple myeloma may be associated with severe renal tubular injury which is usually ascribed to tubular obstruction by casts of precipitated protein (1). However, Armstrong (154) has found more marked interference with glomerular filtration than with tubular function, suggesting that cast formation is a secondary rather than primary event in the production of renal damage.

The nephrotic syndrome has been reported to appear following bee-sting (116), poison oak dermatitis (22), tridione therapy (155), and during the course of lupus erythematosus (87).

*Necrotizing nephroses.*—The necrotizing nephroses are characterized

clinically by renal insufficiency of varying degree, oliguria or anuria, and moderate or slight proteinuria. The nephrotic syndrome rarely, if ever, appears The tubular injury is evident pathologically in cellular changes ranging from cloudy swelling to outright necrosis and disintegration. Collapse and blockage of tubules, nephron destruction, and associated renal vascular adjustments interfere with filtration and prevent adequate urine formation These conditions have many causes The direct action of such noxious substances as heavy metals, carbon tetrachloride, ethylene, and heme pigments may be sufficient to cause extensive cell death and renal dysfunction. However, most of these agents also give rise to cardiovascular disturbances that may in turn affect renal function and structure. Numerous studies of shock, and experience gained in the care of wounded men, have shown quite clearly that peripheral circulatory collapse is associated with a renal functional impairment that may have fatal consequences if sufficiently prolonged. Van Slyke (156) has recently reviewed the work on these changes in kidney function. Renal blood flow and glomerular filtration rate are greatly reduced in man and animals during shock as the result of marked arteriolar constriction. These changes become irreversible in time, and even if the vascular disorder is promptly corrected, days and even months may elapse before recovery of kidney function is complete. Burnett *et al.* (157, 158, 159) observed diminished urinary concentrating power as long as 49 days after severe shock. Likewise renal extraction and maximal tubular excretion of PAH or diodrast diminish (160, 161). It seems reasonable to believe that protracted anoxia of the kidney subsequent to ischemia may account for these evidences of tubular dysfunction But the kidney seems remarkably resistant to the effects of anoxia. Animals and men may be kept at high altitude or exposed to an oxygen-poor atmosphere for long periods with little or no change in renal function (162, 163, 164) The renal artery may be clamped off for as long as four hours in dogs without fatal consequences (165, 166). Half this time is required to produce fatal uremia in rats (167, 168). The resulting renal lesion is characterized by degeneration and necrosis of the cells of the proximal convoluted tubules (169, 170). In man the renal pathology of shock remains unsettled. Herbut (171), Bell & Knutson (172) and Moon (173) place the site of greatest damage in the proximal segment, whereas Lucké (92) has drawn attention to the frequency with which lesions are found in the lower nephron in conditions complicated by shock.

The immediate causes of renal vasoconstriction during shock are uncertain Trueta and his co-workers (46) have recently suggested that vasoconstriction is mediated through nervous pathways, since they were able to induce marked renal vasoconstriction in rabbits by stimulation of the central end of a divided sciatic nerve or the distal end of a divided splanchnic nerve. Division of the splanchnic nerves prevented the development of renal ischemia during tourniquet shock in rabbits. Beautiful demonstrations of the renal vasculature with radio-opaque dyes revealed that marked cortical ischemia developed during shock or intense neural stimulation. Arterializa-

tion of renal venous blood and a decreased renal circulation time seemed to be consistent with the hypothesis that blood was "shunted" away from the cortex through the medulla. However, careful anatomical studies failed to show a significant arteriovenous shunting system and it was suggested that passive dilatation of the large caliber efferent vessels which leave the juxtamedullary glomeruli to enter the medulla (174) might account for the apparent medullar hyperemia. Other workers, [Cort & Barron (175) and Goodwin *et al.* (176)] have confirmed these observations in dogs, cats, and monkeys, although Taylor & Page (177) failed to prevent vasoconstriction when the kidneys were denervated or the spinal cord was severed at $L_1$, possibly because a humoral agent was also operating. Massive doses of epinephrine may have a similar effect and have been used to produce bilateral cortical necrosis experimentally (178).

There is no functional evidence that arteriovenous shunting normally occurs in the kidney. Reduction in renal blood flow by abdominal compression (130) or drugs (179) does not reduce PAH extraction as one might expect if blood passed directly from the arteries to the veins. Van Slyke (156) and his co-workers failed to find any significant change in PAH extraction in animals during acute experimental shock sufficiently severe to lower renal blood flow to a fraction of normal until enough time had elapsed to permit cellular damage Small shunts may exist, since Simkin *et al* (180) have shown *that* micro-beads too large to pass through capillaries may find their way from renal artery to renal vein in the dog, but it is likely that these channels are relatively unimportant. Furthermore, satisfactory evidence that medullary "hyperemia" occurs has not been forthcoming, and it now seems likely that Trueta's observations are best explained by a widespread intrarenal vasoconstriction preponderantly affecting the cortical arterioles. In this view, blood continues to flow through the relatively low resistant medullary vessels but is excluded from the cortex almost entirely The medulla is thus subjected to a less marked ischemia than the cortex and suffers less damage in consequence when ischemia is prolonged. Under these circumstances the lesions produced might differ from those observed in animals following occlusion of the renal artery.

Bilateral cortical necrosis usually occurs as a complication of pregnancy (181, 182, 183) in association with peripheral circulatory collapse. It seems likely that lesser grades of renal ischemia with tubular functional deficiency and oliguria following abortion also reflect predominantly cortical vasoconstriction (184) Stimulation of the pressor area of the cerebral cortex in cats and monkeys results in renal cortical ischemia (185) and it is well known that emotional (72, 186) and painful stimuli (187) may induce marked renal vasoconstriction in man, with resultant oliguria. Death as a result of cortical necrosis has been observed seven days after electro-shock therapy, without evidence of circulatory collapse (188). Frank shock, then, is not necessary for the development of cortical necrosis, but the relationship to collapse is unmistakable in most instances, giving additional substance to the view that

renal ischemia in shock in man is also more marked in the renal cortex.

The pigment or hemoglobinuric nephroses are characterized by striking lesions in the lower nephron. The kidneys are small and pale, often with congestion of the medulla. Foci of necrosis are found in the cortex limited largely to the distal convoluted tubules. Pigmented casts fill and apparently plug the tubules and collecting ducts, accounting for the "hydronephrotic" dilatation of proximal tubules. In some places, the tubular walls break down, casts are extruded into the interstitial tissue, and phlebitis of neighboring veins develops with thrombosis and formation of so-called "tubulovenous" communications. This lesion occurs typically following intravascular hemolysis due to transfusion with incompatible blood (92, 189, 190), introduction of distilled water during transurethral prostatectomy (191), extensive cutaneous burns (192, 193), paroxysmal hemoglobinuria (194), myanesin therapy (195, 196), and blackwater fever (197, 198). In addition, Bywaters (199) and his associates have shown that muscle injury may result in the release of large amounts of myoglobin into the blood with subsequent lower nephron pathology, uremia, and death. This disorder may follow muscular damage by electricity (200), flogging (201), or arterial occlusion (202) Since circulatory collapse is a prominent feature in the course of nearly all these conditions, the question of shock versus pigment as the major etiologic factor arises at once

On the one hand, workers such as Bywaters (169) protest vigorously against the idea that shock or renal anoxia are of chief importance because, as noted above, it appears that renal ischemia alone usually causes proximal tubular damage, because shock does not develop in many instances, and, finally, because renal tubular lesions may be produced experimentally with heme pigments such as hemoglobin (203) and myoglobin (204). According to these workers renal insufficiency is chiefly a result of tubular obstruction by casts On the other hand, there are now compelling reasons for believing that heme pigments are precipitated in the tubules only in the presence of pre-existant renal damage or of renal dysfunction due to dehydration, shock and the like Recurrent paroxysmal hemoglobinuria may persist for years without evidence of renal damage (60). Amberson and his co-workers (205) administered 50 to 60 gm. of hemoglobin in single intravenous injections (up to 900 gm. total dose) to human subjects even in the presence of shock without ill effect Other workers (206 to 209) have not been able to produce renal lesions with heme pigments in normal, well-hydrated animals. It seems reasonable to conclude that lower nephron nephrosis involves two factors, i e , an appropriate physiologic setting and an effective toxic agent. Whether the peculiar localization of the lesions is a function of the redistribution of blood in the kidney during shock, emphasized by Trueta and others, or a function of the peculiar properties of heme pigments and associated toxic materials, remains unsettled. In any case, the view that neurogenic renal vasoconstriction may play an important part, has excited interest in the possibility of inducing vasodilatation by nerve block. Spinal anesthesia

(158, 210) has been found generally ineffective. Williams (211) has reported diuresis following anesthesia to $D_7$ in one case of oliguria due to Weil's disease, but it is impossible to be sure that this would not have happened in any case. Use of pyrogens to cause renal hyperemia has been suggested (212) despite the serious dangers involved Tetraethylammonium bromide has been recommended for clinical use because it seemed to prevent cortical ischemia in experimental animals (213), but other work (214) has shown that it will produce renal ischemia in normal man and is therefore probably of little use. Dibenamine has a similar adverse effect (215). Alkalinization has been widely urged as a means of promoting solution of the pigment casts, but here again experience has proved that the procedure may have its own dangers (216) and may have little beneficial action. It appears that vigorous treatment of shock, if present, and correction of the various aspects of renal insufficiency are the therapeutic measures of choice.

Carbon tetrachloride is gaining increased recognition as a potent cause of renal damage (217 to 220). As a rule the hepatic disorder caused by carbon tetrachloride overshadows the manifestations of renal dysfunction, but the kidney may suffer greater injury than the liver when the substance enters the body by way of the respiratory tract. Here the entire nephron is affected, though lower nephron localization may be prominent (218).

The heavy metals cause necrotic tubular lesions which predominantly affect the proximal convoluted tubules, the extent of damage apparently depending upon the amount of the material entering the blood. Cell death, destruction of tubules, and calcification of necrotic tissue are prominent findings Man appears to be peculiarly sensitive to the nephrotoxic effects of heavy metals. Brun *et al.* (221) and others (222) have shown that mercurial diuretics interfere with PAH excretion by the tubules in human subjects, but not in the dog. These substances may cause fatal injury in certain instances (223, 224) The discovery that the dithiol, 2,3-dimercaptopropanol, British Anti-Lewisite (BAL), displaces ionic mercury as well as trivalent arsenic from cells with reactivation of poisoned enzyme systems (225), has proved of major importance in the treatment of mercury poisoning in man. Longcope & Luetscher (226) treated 23 patients with intramuscular injections of BAL (300 mg.), 1 to 3½ hr. after taking up to 20 gm. of mercury bichloride. Two or three additional doses of 150 mg. were given during the following 12 hr All recovered, whereas 27 of 86 patients taking more than 1 gm. of mercury bichloride before BAL therapy was available died. Unfortunately BAL does not prevent the renal injury by uranium (227) or cadmium (228)

The renal functional impairment during the course of the necrotizing nephrosis is usually profound. The clearances of inulin and PAH are markedly depressed. Tubular excretion of PAH may cease altogether, and occasionally back-diffusion of PAH seems to occur (229, 230, 231). Evidence that the tubular cells no longer operate effectively in maintaining a concentration differential between blood and urine is found in the tendency of urea reabsorption to increase (232, 233)

## Renal Insufficiency

As noted above, renal insufficiency may result from strictly functional changes (e.g., shock) as well as kidney disease. Since such states may ultimately cause damage, there is obviously considerable overlap between so-called "extrarenal uremia" and renal uremia. Dehydration, sodium depletion (234, 235), or excessive use of alkali (216) appear to be capable of exciting irreversible renal insufficiency. These and other stresses, even though moderate, may be sufficient to precipitate fatal uremia when renal disease is already present (236). In such circumstances, the development of renal dysfunction may be overlooked until too late for correction. The various manifestations of renal disease, such as anemia, may also confuse the picture and mask the presence of intrinsic renal pathology (237). Chemical abnormalities (238) may be the only changes. Gastrointestinal, neurologic, cardiac, and respiratory disorders in uremia are not well understood. The pathogenesis of such anatomic changes as have been detected is by no means settled. For example, the pancreatic lesions consisting of acinar dilatation, flattening of lining epithelium, and inspissation of secretion, recently described by Baggenstoss (239), may be attributed to excessive vomiting or to some nonspecific inhibition of pancreatic secretion.

Certainly the alteration in plasma electrolytes during acidosis due to kidney disease must lead to serious disturbances of intracellular electrolytes, as the significant studies of Mudge & Vislocky (240) demonstrate. Moreover, it is possible that toxic agents of some kind are retained by the kidneys. Phenol appears to mount in the blood chiefly as the result of the activity of intestinal bacteria, possibly *proteus vulgaris*, since treatment of uremic dogs with streptomycin appears to keep the blood phenol concentration within normal limits, whereas phthalylsulfathiazole has no effect. Although phenol does tend to accumulate, there is no evidence that it has anything to do with the symptomology of uremia (241, 242). There is little doubt that potassium may accumulate in the blood, reaching toxic levels and even causing death. In more than one-half of 26 patients with severe renal insufficiency Elkinton, Tarail & Peters (243) found abnormally high serum potassium concentrations, with electrocardiographic evidence of intoxication before death in four [peaked T-waves, prolonged QRS interval, elevation of the S-T segment, or cardiac arrest (244)]. Diminished glomerular filtration was the principal cause of potassium retention in these patients. Keith & Osterberg (245) have found that such patients are usually unable to excrete potassium efficiently following ingestion of a standard dose. A small number seem to have increased tolerance to potassium.

Elkinton (243) found depression in the serum potassium in four members of his series though there was no evidence of augmented renal excretion. However, the discovery by Berliner *et al.* (246) and Mudge *et al.* (247) that the tubular cells may secrete potassium indicates the possibility that potassium loss may result from overactive tubular excretory mechanisms. Sherry *et al.* (248) have reported such a case characterized by hypopotassemia, hypochloremia, hypotension, transient muscular weakness, and electro-

cardiographic abnormalities consisting of flattened T-waves, depressed S-T segment, and bradycardia. The electrocardiogram may be affected in uremia also by the development of pericarditis or disorders of calcium-phosphate metabolism (249, 250).

Important contributions to our knowledge of disturbances in calcium and phosphate metabolism during various forms of renal insufficiency have been made by many workers during recent years, in particular by the group working with Fuller Albright at Massachusetts General Hospital in Boston This is a most confused and complex field of study. The syndrome of "renal rickets" has been recognized for many years as a disorder of bony development occurring especially in children during the course of chronic renal disease with renal insufficiency and persistent acidosis. Retention of phosphate as a result of impaired glomerular filtration is believed to play a major role in producing hypocalcemia, perhaps in part by interfering with normal intestinal calcium absorption Post-mortem examination has revealed the frequent occurrence of parathyroid hyperplasia which Albright (251) believes is secondary to the hypocalcemia Although the pathology of bone resembles rickets radiologically, it presents the histologic features of osteitis fibrosa cystica, typically found in primary hyperparathyroidism. In addition, widened osteoid seams occur, suggesting coexistent osteomalacia or rickets. Albright and others attribute these changes chiefly to the ever-present acidosis, though possibly hyperactivity of the parathyroids is also involved. Other abnormalities of renal function may give rise to quite definite osteomalacia. Albright and his co-workers (251, 252) have been largely responsible for the clarification and definition of these conditions.

These investigators have described a group of adult patients in whom failure of the renal tubular base-sparing mechanisms of acid excretion and ammonia formation leads to excretion of a persistently alkaline urine containing excessive amounts of sodium, potassium, and calcium, with the production of a severe chronic acidosis in association with hyperchloremia The plasma concentration of calcium is usually maintained within normal limits whereas the plasma phosphate concentration is reduced and serum alkaline phosphatase elevated. These are the typical biochemical changes in osteomalacia Definite histologic changes of osteomalacia have been found in two cases of this disorder (252) Clinically the bone changes are manifested as Milkman's syndrome, i.e , bilaterally symmetrical pseudo-fractures which appear as ribbon-like zones of decalcification in otherwise normal looking bone. These lesions are believed to be due to minor breaks in the bone cortex with subsequent formation of callus that fails to undergo calcification. Le May & Blunt (253) have pointed out the correspondence between the sites of the lesions, which may be quite numerous in any single individual, and the location of the main arteries which lie on the bones. They suggest that the osteomalacic bone may yield to the constant pressure of these vessels. Albright attributes the bony defect to calcium depletion secondary to the failure of the kidney to conserve all basic ions. In some instances, dangerous

and perhaps even fatal hypopotassemia has developed. Correction of the acidosis with alkaline therapy results in dramatic clinical improvement, clearing of Milkman's syndrome, and reduction in urinary calcium excretion.

A somewhat similar condition of persistent acidosis in association with excretion of alkaline urine has been reported in children under one year of age (254 to 257). In these cases no bone pathology or calcium-phosphorus imbalance was evident. As in the renal acidosis of Albright, there may be nephrocalcinosis, or calcium deposits in the medullary pyramids, and hyperchloremia. An anomalous case in an infant has been reported by Pratt, Geren & Neuhauser (258), who found renal acidosis, without other evidence of renal functional impairment, in association with hypercalcemia, reduced urinary output of calcium, nephrocalcinosis, parathyroid hyperplasia, and osteitis fibrosa.

It seems likely that "renal acidosis" may account for certain cases of "renal rickets" in which the serum phosphorus level is not elevated despite marked impairment of glomerular filtration (259).

Another type of renal acidosis is encountered in Fanconi's syndrome (260). Here there are unusual urinary losses of various amino acids, glucose, and phosphate as the result of defective tubular reabsorptive mechanisms. Base is lost in the urine in association with the excessive organic acid excretion despite effective ammonia production. Acidosis often occurs The serum calcium level is usually normal, the serum phosphate concentration low, and alkaline phosphatase increased. Bone changes consistent with osteomalacia have been described (261). Nearly all the amino acids are excreted in excess, and in at least one case marked cystinuria occurred In congenital cystinuria there is likewise excretion of other amino acids (262). The cause of the bone changes is obscure since they may occur in the absence of acidosis and the serum phosphate level may change only after osseous pathology has developed (263).

Numerous reports (264 to 270) of nephrocalcinosis and subsequent renal insufficiency following administration of large doses of vitamin D have appeared in the last few years. Provided there is an adequate intake of calcium, 100,000 I.U. of vitamin D per day is sufficient to induce widespread metastatic calcification of tissues. Peritubular deposits of calcium appear in the renal interstitial tissue and destruction of nephrons may lead to fatal uremia. Burnett *et al.* (216) have described a syndrome of hypercalcemia without hypercalcuria or hypophosphatemia, normal serum alkaline phosphatase concentration, mild alkalosis, marked renal insufficiency, and calcinosis following an excessive and prolonged intake of milk and alkalis.

The treatment of uremia is largely symptomatic. Electrolyte imbalances may be adjusted by appropriate parenteral and peroral therapy In patients with anuria or marked oliguria there is often a tendency to administer excessive amounts of water and salt, sometimes causing death from pulmonary edema (271, 272). Hence, careful control of therapeutic measures is vital to successful management. Borst (273) has recently emphasized the need for

maintaining an adequate caloric intake and for reducing, in most patients, the intake of phosphorus and potassium. To achieve this end, Bull and his co-workers (274) recommend administration of an emulsion of peanut oil, glucose, and water by intragastric drip.

During the past three years, widespread interest has been aroused in methods of vividialysis as a means of temporarily replacing functionless kidneys. A voluminous literature has resulted which it is impossible to review in detail here. In general, various modifications of three procedures have been employed, viz., peritoneal irrigation (275, 276), intestinal lavage (277, 278), and the so-called artificial kidney (279, 280, 281). It has been demonstrated that the nonprotein nitrogen of the blood is lowered, electrolyte disturbances corrected, and the water balance adjusted efficiently by these measures. However, all require constant attention by skilled personnel and none is without certain dangers. In the process of peritoneal lavage, the peritoneal cavity must be entered surgically, a sump drain inserted and an irrigating apparatus maintained. In uremia, intestinal organisms readily traverse the intestinal wall (282) and fatal peritonitis may ensue. Hence, prophylactic chemotherapy is necessary. Considerable difficulty has been encountered in placing a tube in the small intestine, in recovering the perfusing fluid, and in controlling electrolyte exchange during intestinal lavage All forms of the artificial kidney depend upon cellophane as a dialyzing membrane and on circulation of blood through the apparatus from artery to vein following heparinization. The obvious hazards here include infection and hemorrhage Improper use of dialyzing fluids may lead to overhydration, dehydration, or maladjustments of electrolytes These devices are valuable experimental tools which, with further development, may prove useful adjuncts in the treatment of uremia. It is impossible to assess their value at present, owing to the difficulty in determining prognosis in individual cases (283). Conservative treatment seems to be equally or perhaps more effective in prolonging life and in regulating plasma composition.

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# NUTRITION IN MEDICINE[1]

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Fundamentally, nutrition is of vital importance for the growth and maintenance of all body cells. It enters into all aspects of health including mental health. Nutrition is concerned with food and the ingredients of food known as nutrients which are necessary for health, with the physiologic action of these nutrients, and with the consequences of not having effective cell concentrations of any of the 50 to 60 nutrients now known. In our present day civilization in which the prevention, control, and treatment of most of the serious infectious diseases are well in hand, nutrition is the single most important environmental factor affecting the health of Americans. Such a statement does not refer in any way to the classical nutritional deficiency diseases of scurvy, beriberi, or pellagra, which are of relatively minor importance in this country today, thanks to the intelligent and prompt application of nutritional findings important to the prevention and treatment of these diseases. But it does refer to the importance of nutrition, including what one might call cellular nutrition, to the so-called degenerative diseases including the cardiovascular renal diseases and cancer; it does refer to the role of nutrition in diseases of the liver and the hematopoietic system; it does refer to the dangers of obesity to good health; and it does refer to the potentialities of antinutrients and antimetabolites in the etiology and treatment of disease. Hence, we feel justified in stating that in present day America, nutrition is the single most important environmental factor affecting health.

Any discussion of reasonable length dealing with advances in nutrition of importance to medicine must be confined to a few subjects. The balance of this review will be confined to discussions of nutrition in relation to hypertension, to vitamin $B_{12}$ in hematopoiesis, and discussions concerning potassium in nutrition and fat emulsions as a part of parenteral nutrition.

## Hypertension

The multiplicity of the measures advocated for the treatment of hypertension testifies to the difficulties attendant in the search for an effective method of treatment of this major clinical problem. Diet is among the many procedures that have been stressed in recent years.

Goldring (1) has pointed out that a major consideration in the evaluation of any measures used in the treatment of hypertension is the difficulty of obtaining adequate criteria by which to assess clinical improvement. Blood

[1] This review covers primarily the period from January, 1948 to July, 1949

pressure data are notoriously misleading in that the vascular complications of the disease may proceed unchecked to a fatal issue despite restoration of blood pressure to normal levels. The evaluation of changes in papilledema, heart size, and the electrocardiogram on any therapeutic regimen cannot be accurately undertaken until sufficient information on the spontaneous alterations of these evidences of vascular disease in an untreated control group has been acquired. Subjective improvement on a therapeutic regimen, though gratifying to patient and physician, fails to indicate that the natural course of the disease has been modified in any manner.

The dietary treatment of hypertension today consists primarily of low sodium diets with a caloric content such as to treat or prevent obesity. While the importance of avoiding or treating obesity has been recognized for a long time, the emphasis on low sodium diets is a recent development stimulated, no doubt, by the work of Kempner (13) on the "rice diet." Sodium restriction in the treatment of hypertension was advocated, however, several years before the "rice diet" became popular Allen (2), who was one of the first in this country to call attention to the importance of low salt diets in treating hypertension, summarizes this early work as follows (3):

> ... salt restric-
>
> ciently thorough, but chiefly because their basic theory of chloride retention as the cause of hypertension was easily disproved . . . . Our own work . . . developed from observation of a case of congestive heart failure with severe edema for which the ... The improvement of the ... nded to other ... twenty cases. ... our years.

Grollman *et al.* (4) and others (5) have also pointed out that salt restriction has been advocated since the early twentieth centry, but that the early investigators attributed beneficial effects to restriction of the chloride ion, and that the failure of many to confirm these findings arose from the employment of diets not sufficiently depleted of sodium ion

The relationship between sodium chloride depletion and the hypotension of Addison's disease has long been recognized A considerable number of experiments serve to confirm the hypertensive effect of sodium chloride administration under certain conditions, as well as the opposite effect of salt deprivation. Selye and co-workers (6) showed that the experimental hypertension induced in rats by combined DOCA (desoxycorticosterone acetate) and salt administration could not be reproduced when DOCA alone was given. Renal damage consisting of hypertrophy of the glomeruli, capsular fibrosis, and hyalinization and necrosis of the walls of renal arterioles could be produced by the combined DOCA-sodium chloride regimen, but not with DOCA alone. Grollman & Harrison (7) produced a decided reduction in the blood pressure of rats with experimental hypertension by employ-

ment of low sodium diets and demonstrated prolongation of life span in these animals when long term, low sodium diets were administered.

Knowlton and co-workers (8), in a recent confirmation of some of the findings of Selye just cited, compared the results of combined DOCA and sodium chloride administration with DOCA administration alone in both normal rats and rats rendered nephritic by rabbit antirat kidney serum. They found that although normal rats responded to DOCA and sodium chloride administration with the production of cardiac hypertrophy and adrenal cortex lesions, that nephritic rats responded in a similar manner but with the development of arterial hypertension as well. When DOCA without sodium chloride was given to these two groups, such changes could not be demonstrated in either group. The potentiating action of the sodium ion (9) of saline (10) in experimental hypertension produced by DOCA has been confirmed.

In an interesting experiment on chicks on various diets with and without added salt, Krakower & Heino (11) demonstrated that the average mean pressures of birds treated with additional salt were higher consistently than those treated without salt, with the sole exception of a group of older birds fed ad libitum with very high (15 per cent) salt intake, in which the blood pressure tended to be depressed.

These results were confirmed by the findings of Lenel and co-workers (12) in young chickens, in which the drinking water was replaced successively with 0.9 per cent and 1.2 per cent saline. Blood pressures rose when saline replaced tap water and fell when the latter was restored as the source of fluid. The degree of pressure elevation seemed to correlate with the concentration of the saline within the limits of the two solutions used. Hyperplasia and proliferation of glomerular tufts of kidneys resulted. The mechanism of the hypertensive action of the saline is not clear, but seems to suggest an implication of the adrenal cortex in the pathogenesis of hypertension.

Utilizing the rice and fruit juice diet, suggested by the clinical studies of Kempner (13), Dick & Schwartz (14) observed a consistent fall in blood pressure and nonprotein nitrogen (NPN), as well as weight loss in a group of 11 dogs rendered hypertensive two to four years previously by streptococcus injections. Whether results attained could be attributed to the low salt, low protein, or other factors could not be stated by the authors. Possible alterations in the excretion of sodium and chloride ions by the hypertensive kidney as well as evidence suggesting the implication of the adrenal cortex in hypertension have been reviewed by Bradley (15).

In contrast to the data just cited favoring the pre-eminence of sodium as a hypertensive factor, other observations are available which would tend to minimize the role of sodium as an influence in the maintenance of hypertension in comparison with the role of the adrenal cortex. Loeb *et al.* (16) demonstrated that hypertension could be produced in patients with Addison's disease with DOCA. Perera *et al.* (17) reported cases of induced hypertension not only in Addison's disease but also in individuals

with normal adrenals during DOCA administration. In another report (18), Perera cites the case of an hypertensive patient who subsequently developed normal blood pressure after the onset of Addison's disease. Hypertensive levels could be restored only when sodium chloride plus DOCA were administered, but not with sodium chloride alone.

Grollman (19) failed to demonstrate by sodium restriction any reduction of hypertension experimentally produced in dogs. The fact that the blood levels of sodium and chloride are the same in hypertensive dogs as in normal dogs, may explain the failure of sodium restriction to reduce blood pressure in these animals. The author concludes that hypertension is not always simply a result of retention of sodium.

*Clinical experiences with diets.*—In an early study on patients, six hypertensive individuals were treated by Grollman *et al.* (4) with diets of 2,000 kcal. containing less than 1 gm. of sodium chloride but adequate in protein. Reduction of the blood pressure to normal levels were attained in two individuals, moderate blood pressure reductions were achieved in three individuals, and no change was observed in the sixth patient. Restoration of sodium chloride intake resulted in restoration of hypertensive levels in the two individuals in the first group. Perera & Blood (20) compared the effects of dietary sodium restriction (0 25 to 0.35 gm per day) over a 24-hr period in 12 control subjects and in 12 hypertensive individuals free from renal impairment. Control subjects exhibited both weight loss and increased diuresis during the sodium-restriction period; the hypertensive subjects did not experience such changes Sodium and chloride clearances were reduced in the hypertensive but not in the control group during sodium restriction No change in the blood pressure of either group occurred. The authors' interpretation is that hypertension is associated with a disturbance in salt and water metabolism either on a primary renal basis, or as a result of an altered adrenal cortex-renal relationship. These investigators, in another series of experiments (21), found that rigid sodium restriction (250 to 350 mg. sodium per day, plus 70 gm of protein, plus 1,700 to 2,000 kcal ) in six uncomplicated cases of hypertension lowered the "resting" blood pressure (arbitrarily defined as the lowest of six determinations in the morning) but not the "casual" pressure (random determinations taken during the day). Response to cold pressor tests was unchanged. Neither the cardiac output nor circulatory volume was affected DOCA administration to these patients during sodium restriction failed to elicit pressor responses, which ordinarily occurred during moderate sodium intake. On the basis of the dichotomy of response of "resting" and "casual" blood pressures to dietary and hormonal therapy, the authors postulate different underlying mechanisms, comprising an intrinsic (humoral) factor which may respond to sodium restriction and an "extrinsic" (neurogenic) factor often relieved only by neurosurgical measures

Stead and co-workers (22), in an attempt to elucidate further the effect of salt depletion in hypertensive individuals, studied 12 hospitalized patients

suffering with varied degrees of hypertensive vascular disease and renal involvement. The effect of alternate periods of salt deprivation and salt administration (with adequate protein allowances) was determined on both random blood pressure and "TEAC floor" (the lowest blood pressure following tetraethylammonium chloride administration); the latter was assumed to represent the blood pressure constituted by humoral and peripheral vascular components, with the neurogenic component eliminated. In five patients, salt deprivation resulted in a significant reduction of the TEAC floor (humoral component), but very little reduction in the random blood pressure, suggesting a compensatory rise in the neurogenic component of the latter. Salt deprivation failed to reduce either the TEAC floor or random blood pressure in the other seven patients, despite a demonstrable fall in serum sodium The group of five responding comprised chiefly cases of benign hypertension, whereas the group resistant to salt deprivation comprised cases of malignant hypertension, renal failure, or both The inference drawn is that sodium restriction may produce reduction in the humoral component of the blood pressure in benign hypertension (under hospital conditions) but not in cases of advanced hypertension with renal insufficiency

Extensive clinical application of dietary therapy for hypertensive patients has been reported by Kempner since 1944 (13, 23) utilizing the "rice diet," which consists of white rice (250 to 350 gm.), fruit, and fruit juices. Calories up to a level of 2,000 or more are supplied by the use of white sugar or dextrose, and vitamins are prescribed. Except for the traces of protein furnished by fruit, rice is the only source of protein and provides about 20 gm The diet contains less than 5 gm. of fat, and fluid is limited to the 700 to 1,000 cc. supplied by the fruit juice. The use of vegetables, vegetable juice, or any other source of nutrients is forbidden. The use of canned fruits or fruit juices containing more than white syrup is also forbidden. This "strict rice regimen" is subject to later supplementation with small servings of meat and vegetables, depending on the degree of improvement manifested by the patient. Of 500 hypertensive individuals, 46 per cent of whom were also suffering with renal complications, improvement was manifested in 65 per cent either by a fall in the mean blood pressure (systolic plus diastolic divided by two) of 20 mm Hg or more, or by changes for the better in the electrocardiogram, status of the retina, or heart size One hundred twenty-five of the 500 enjoyed a return of their blood pressures to normal levels Of the 500 *patients studied, 305 had been followed for more than 35 days* The importance of rice as the chief source of protein is stressed, and it is stated " . . as far as the metabolism of kidney cells is concerned, rice protein cannot be indiscriminately replaced by other protein " The reviewers know of little evidence to support such a statement.

Of interest with regard to Kempner's preference for rice as the sole source of protein is the observation of Sure (24) that the protein efficiency of polished rice, expressed as gain in weight in animals per gm. of protein intake, was 158 per cent greater than that of enriched wheat flour, when rations of the

two nutrients were fed to a group of rats at equal levels of protein intake during a ten-week period.

Bryant & Blecha (25) have obtained results which would seem to indicate that neither qualitative nor quantitative restriction of protein is necessary in order to obtain satisfactory results in all patients. In their series of 100 ambulatory patients treated with diets of 2,200 kcal., 70 gm. of protein, 80 to 175 gm. of fat, and 130 to 230 gm. of carbohydrate with 200 mg. of sodium, 35 per cent of patients experienced lowering of blood pressure and a majority enjoyed relief of related symptoms.

Very little difference in results of the rice diet and a low sodium diet adequate in protein was found in the carefully studied, though admittedly small, series of Rosenberg *et al.* (26), who compared the effects of the two diets in four patients. Systolic and diastolic blood pressures fell in two of these patients on both diets. There was only very slightly greater fall in blood pressure on the rice diet than on the low sodium diet in these patients. Four additional patients were treated with only one of the diets, with improvement in the blood pressures of three of them. There was no improvement in clinical symptoms in any of the five patients whose blood pressures fell during therapy. Although the dietary regimen was maintained for a minimum of four weeks in all patients, longer periods may be necessary in view of Contratto's observation (27) that a maximum fall in blood pressure in some of his cases did not occur for from six weeks to three months Rosenberg concluded that these diets are not of sufficient value for routine use in hypertension.

Contratto & Rogers (27) observed a fall in systolic and diastolic blood pressure in 70 per cent of their group of 34 nonhospitalized patients treated over a six-month period with the rice diet. Lowest readings occurred between the sixth week and third month The incidence of changes in eye grounds, electrocardiogram, or heart size is not recorded, nor is the incidence of changes in subjective complaints, although all patients enjoyed an improved sense of well-being. No changes in the blood urea nitrogen, chloride, total protein, or albumin-globulin ratio were noted, although a decrease in the blood cholesterol was noted in some cases Included are the protocols of five of the patients, so treated, in whom blood pressure levels seem to have remained constantly high prior to the institution of the rice diet. Helpful measures to encourage the patient to adhere to the diet, a problem of considerable importance (28), are set forth The authors feel that the rice diet is the most hopeful treatment available at present for essential hypertension

Schroeder *et al.* (29) were unable to note any consistently beneficial effect from the rice diet after preliminary control observations. Of seven patients treated with the rice diet, three exhibited moderately lower blood pressures, whereupon addition of sodium chloride to the diet of two of these patients did not result in elevation of blood pressure On the basis of their observations with a group of hypertensive patients, Williamson & Schwartz (30) found that significant reduction in blood pressure and symptoms results in a

considerable number of patients from hospitalization per se, and that among the group not so responding, a certain number respond favorably while on the rice diet. Supplementation of the rice diet of three of four patients who had exhibited lowered blood pressures while on that diet alone, with protein *in the form of a desalted milk product did not result in change in blood* pressure or symptoms. Addition of 10 gm. of sodium chloride to the diet of these four patients without the patients' knowledge resulted in elevation of blood pressure in two of them.

Loofbourow *et al.* (31) studied the effects of the Kempner rice diet on a group of 56 patients with hypertension treated on an outpatient basis. Sixteen (28 per cent) were strict adherers, 20 (36 per cent) were moderate adherers, and the remainder were nonadherers to the diet. The results of the last mentioned group were discarded. A significant drop in blood pressure (reduction of median diastolic pressure of 20 mm or more) occurred in 37 per cent of those who adhered strictly to the diet, and a significant drop occurred in 15 per cent of the moderate adherers to the diet. Other results have been deferred for later publication. Evaluating their results from another point of view, 9 patients, or 16 per cent of the entire group for whom the diet was prescribed, benefited from the therapy according to the authors' criteria.

Megibow *et al.* (32) have advocated an intensive program designed to produce salt depletion by combining low salt diets with mercurial diuretics, which effected significant reductions of blood pressure in five of their eight patients Regression of retinal changes and relief of headaches also resulted in most of the group Increased lability of the blood pressure and enhanced response to tetraethylammonium chloride (TEAC) after the regimen were noted, suggesting that a desalting program preliminary to splanchnicectomy may augment the beneficial effects of the latter procedure. The lowering of the blood pressure is felt to be associated with altered corticoid function (33).

Excellent reviews dealing with the role of low salt diets in hypertension have recently appeared (5, 34). The authors of both reviews manifest a conservative viewpoint with regard to the efficacy of dietary measures. Among the better controlled clinical studies of low sodium diets in hypertension are those of Viersma (35) of Holland, cited by Schroeder (34), in which the beneficial effects seem to be limited to milder cases of the disease. Kempner's work has been the subject of criticism (5, 34) because of the lack of adequately controlled observations An interesting observation of Schroeder *et al.* (36) is that women with so-called "pseudo-Cushing's syndrome" (having many but not all of the signs diagnostic of Cushing's syndrome) exhibit the most gratifying response to low salt regimens

*Difficulties with low sodium and rice diets.*—Emphasis has been placed on the dangers attendant on the use of the rice diet and other salt-depriving regimens. Schwartz & Merlis (37) have presented evidence indicating the rice diet advocated by Kempner to be nutritionally inadequate, in so far as

the maintenance of nitrogen equilibrium is concerned. Six normotensive adults, after a period of low protein intake, were placed on nitrogen balance studies while on the rice diet. During the entire eight-day period on the diet, the patients exhibited negative nitrogen balance and weight loss. A fall in serum cholesterol was also noted. One hypertensive patient who was treated with the rice diet for 90 days (*with resulting clinical improvement*) exhibited negative nitrogen balance on the thirtieth, sixtieth, and ninetieth days of the therapeutic period. Other investigators (38) have confirmed the finding of negative nitrogen balance in patients on the rice diet.

The danger of either precipitating or exacerbating azotemia as a result of sodium chloride restriction is ever-present in chronic renal disease, in which the damaged kidney may lose its ability to conserve sodium or chloride ions, although this rarely progresses to the point of simulating adrenal cortical insufficiency. The experience of MacGuire (39) and Soloff & Zatuchni (40) would indicate that the blood urea nitrogen be closely followed particularly in patients with renal disease. Kempner has stressed the importance of following the serum and urine chlorides of patients treated with the rice diet (41).

Sodium restricted regimens, including the Kempner diet, have been reported to produce significant decreases in glomerular filtration rate and renal blood flow (42). In addition to the possible complications resulting *from prolonged severe restriction of sodium and of protein (in the rice diet)* one must be aware that many low sodium diets, and the rice diet in particular, are grossly inadequate from the viewpoint of modern nutrition Hence, patients on such diets must be followed with considerable care

Landowne (43) and others (27, 28) have remarked on the problems encountered in attempting to attain patients' adherence to the truly low sodium diets. Indeed, most reports state that a certain number of patients find it impossible to follow either the rice diet or low sodium diets of other composition. Contratto's experiences and suggestions in this regard may be of great value (27). A propos of technical difficulties involved in the employment of these diets, mention should be made of a new table of sodium and potassium contents of food and water as analyzed by the flame photometer (44).

In an effort to effect sodium restriction by measures other than dietary, use of cation-exchange resins was suggested by Dock (45) in the hope that such resins taken by mouth might prove of value in depleting the body of sodium. Limited studies (46) would indicate that certain resins under investigation are nontoxic within certain dose ranges and effective in raising fecal excretion of sodium and potassium ions, although data are not yet available regarding effects on other electrolytes.

In reflecting upon the data presented thus far, obtained from both experimental work with animals and clinical observations, one may conclude that both the rice diet and other extremely low sodium diets exert a hypotensive action in a limited number of subjects. Whether the sodium restric-

tion per se is responsible for any beneficial results obtained cannot be st from the observations thus far cited. The fact that sodium-free diet: unpalatable and tend automatically to discourage food intake, coupled the demonstration of Keys *et al.* (47) that semistarvation may of itself duce a reduction in blood pressure and heart size, serves to compl evaluation of one isolated variable such as sodium restriction. It w therefore, seem proper to consider the role which caloric restriction, pendent of sodium restriction, might exert on blood pressure.

*Influence of caloric reduction on hypertension.*—Justification of a tl peutic regimen for hypertension based on diets of restricted caloric in invokes the following questions: (*a*) Is the incidence of essential hyperte significantly greater in obese individuals than in those of normal we (*b*) To what extent does caloric restriction influence the clinical cour patients with hypertension?

A considerable amount of older evidence indicates that essential hy tension occurs more commonly in obese individuals than in persons of weight. Ideal weight of an adult was originally defined as average weig age 30 for any given height for each sex (48). More recently the age us defining "ideal weight" has been reduced to 25 years (49, 50). Further stantiation of the correlation between obesity and increased inciden hypertension has been afforded by the recent survey of Levy *et al.* Examination of the medical records of more than 22,000 army office vealed a higher incidence of subsequent hypertension in overweight viduals than in the control group, although overweight alone did no nificantly increase the death rate from cardiovascular disease. Alth Robinson, Brucer, & Mass (52), utilizing the ponderal index (weig pounds divided by height in inches) as a criterion of underweight or weight, found that hypertension was considerably more frequent a obese than undernourished individuals, Robinson & Brucer (53) subsequ found hypertension to be a function of body build (ratio of chest cir ference to height) rather than obesity per se. The incidence of hyperte was highest in those of broad build, and lowest in those of linear b Increased incidence of obesity was also found in individuals of broad b Thus, 37 per cent of broad individuals were found to be obese whereas 3 per cent of linear individuals were obese. In any weight group, the b chested individuals were found to have the highest blood pressures. W only one type of body build, the linear group, could obesity and blood sure be correlated. One infers from this study that the simultaneous dev ment of hypertension and obesity results simply because both condi are more prone to occur in individuals of sthenic habitus.

Perhaps the most accurate method of ascertaining the presence o sence of obesity, though not too readily applicable to routine use, i determination of the specific gravity of the individual Since fatty tissu a lower specific gravity than actively metabolizing muscle tissue, this me serves to detect the presence of excess fat. As a result of weighing sul

in air and water, thereby determining the individual's specific weight (weight per unit volume), Welham & Behnke (54) have effectively demonstrated that overweight and obesity are not necessarily synonymous phenomena Keys (55) has pointed out that overweight may connote: (*a*) excess fat, (*b*) broad skeleton with short spine, or (*c*) considerable muscular development. Which of these is the type of overweight associated with increased morbidity and mortality is yet to be determined.

The effect of different degrees of both voluntary and involuntary caloric reduction in the diets of normal weight as well as obese individuals has been studied. Adlersberg, Coler, & Laval (56) observed an average fall in blood pressure of 32/16 in 72 per cent of a series of 54 obese, hypertensive patients on a 1,200 kcal. diet. All patients studied exhibited subjective improvement after weight reduction, regardless of blood pressure response. Fifteen patients were available for a follow-up study three years later. Those who maintained their initial weight reductions experienced a lower incidence of reversion to initial high blood pressure levels than those who failed to do so. No improvement in the vascular state of the retina was noted. Leyton (57) observed lowered blood pressures in individuals maintained on 1,600 kcal. diets during internment in a German prison camp Lups & Francke (58) noted systolic and diastolic blood pressures to be definitely lowered during a starvation period in Holland Seventy-seven per cent of the hypotensive, 47 per cent of the normotensive, and 25 per cent of the hypertensive individuals exhibited increased blood pressures five months later, after food supplies became more available, coincident with weight gain in 80 per cent of the population. A similar observation was made by Nieuwmeijer & Brandsma (59) among Dutch factory workers. Keys, Henschel, & Taylor (47) reported measurements of heart size and function in 32 young, normotensive adults at rest, before, during, and after a six-month period of semistarvation, during which one fourth of the body weight was lost. During the experimental period, heart size and stroke volume decreased; and there was an average drop in blood pressure of 12/6. Venous pressures fell 50 per cent, and bradycardia developed. Most cardiovascular functions were restored by the thirty-second week of nutritional rehabilitation. Heart failure was imminent only during the period of early rehabilitation, but at no time during recovery were hypertensive blood levels noted Brozek, Chapman & Keys (60) have contributed an interesting review of studies on the effect of starvation on blood pressure and cardiovascular function during World War II. The Leningrad study, which included both sexes and all adult ages, during and after the siege of that city (1941 to 1942) is summarized During the starvation period, not only did hypertensives improve subjectively and objectively, but there was also a decline in the incidence of cardiovascular disease Similar observations by different investigators during periods of general starvation or semistarvation in Holland, Germany, and France, some of which have been described in preceding paragraphs, are also cited. In European experiences with recovery from starvation, cases of poststarva-

tion hypertension were reported; and in Leningrad, hypertension after the famine ended became a serious medical problem. The incidence of hypertension among the population rose sharply, as did complications therefrom. Not only the number of hospital admissions for hypertension, but also the incidence of hypertensive cardiovascular disease at necropsy increased sharply. Although data are not available regarding the sodium intake, sodium is not believed to have been limited. What role nondietary factors, such as emotional stress, may have contributed to the rise in incidence of hypertension is not discussed. Relating these observations to current clinical application, the authors conclude that use of the Kempner diet (13) may be justifiable in the severe forms of hypertension, but that a reduction diet alone should suffice in the milder forms of the disease. In this regard, McLester (61) has discussed criteria for weight reducing regimens.

In summarizing the data available, one is led to conclude that at the present time, the dietary treatment of hypertension offers a degree of promise to certain groups of patients. It is of the same order of therapeutic effectiveness, or somewhat better, than the various types of sympathectomies. Evidence available suggests that diets rigidly restricted in sodium content may benefit some of the patients with more benign forms of the disease. Weight reduction is of value to obese individuals with hypertension in that the added load imposed by the adipose tissue is lessened. The more precise selection of patients who may be expected to derive the greatest benefit, the optimum level of sodium, protein, and calories in the diet, the possible additive value of mercurial diuretics or resins as salt-depleting agents are a few of the many unsettled problems which merit further investigation. Not until larger groups of patients have been studied under more carefully controlled conditions than in the past, with due regard for such factors as the spontaneous fluctuation of blood pressure, the response to suggestion and psychotherapy, the effects of bed rest, the necessity for carefully supervised control periods prior to the therapeutic period, and the selection of completely objective criteria of improvement, will one be able to draw more definite conclusions.

## Vitamin $B_{12}$

*Vitamin $B_{12}$ in pernicious anemia.*—Simultaneous with the publication of the report of the isolation of crystalline vitamin $B_{12}$ from liver extract (62), West (63) reported the successful results of treatment of three cases of pernicious anemia with this compound. The doses used, 3, 6, and 150 µg. respectively, were all effective and are of infinitesimally small magnitude when compared with the quantity of refined liver extract required. The ratio of potency of vitamin $B_{12}$ to the refined liver extract used as a standard for assay purposes is estimated to be about 10,000 to 1. The specificity of hematopoietic and clinical response to such amazingly minute quantities of vitamin $B_{12}$ constitutes strong evidence for the belief that it might indeed be the long-sought-for antipernicious anemia principle. West gave four patients

single injections of amorphous concentrates of vitamin $B_{12}$ of a potency equivalent to 2 to 4 μg. of the crystalline substance, and noted marked hematologic response, whereas three patients receiving the equivalent of 1 μg. or less of vitamin $B_{12}$ manifested weak responses or none at all.

Berk *et al.* (64) have reported the effectiveness of parenteral vitamin $B_{12}$ in producing an hematologic remission and neurologic improvement in a patient with pernicious anemia who had manifested hypersensitivity to both hog and beef liver extracts. No allergenic effect of vitamin $B_{12}$ was noted. The specificity of vitamin $B_{12}$ for at least the "biochemical" stages of neurologic involvement was demonstrated by the relapse of the latter during cessation of therapy with subsequent remission when vitamin $B_{12}$ was resumed.

Hall & Campbell (65) reported prompt hematologic response in six patients with pernicious anemia following treatment with 25 μg. intramuscularly of vitamin $B_{12}$ weekly. Bone marrow cellular appearance returned to normal in 48 to 90 hr.; glossitis disappeared in the four patients thus afflicted. Of two patients with subacute combined degeneration, one showed no improvement with 100 μg. over a 62-day period, but the second exhibited remarkable improvement with 75 μg. over a 33-day period.

Numerous reports have subsequently appeared confirming the effectiveness of vitamin $B_{12}$ in the treatment of the anemia (66 to 73), the neurologic lesions (68, 69, 73, 74), and the oral lesions of pernicious anemia (70, 74, 75, 76). West & Reisner (69) found the minimal effective intramuscular dose to be 1 μg. daily, which is in agreement with the dose cited by Bethell *et al.* (66), who have reported remission of signs of pernicious anemia in four patients treated with as little as 1 μg. parenterally per day. The latter workers also showed that vitamin $B_{12}$ is inadequately absorbed in patients with pernicious anemia. This was done by assaying fecal extracts of untreated pernicious anemia patients, and demonstrating that the quantity of LLD (*Lactobacillus lactis Dorner*) factor (presumably identical with vitamin $B_{12}$) present would be sufficient to produce a remission if injected intramuscularly. Callender *et al.* (77) have carried this type of experiment one step further. A fecal extract obtained from a patient with untreated pernicious anemia was injected daily over a five-day period into a patient with untreated pernicious anemia, and a hematologic response, including reversion of the bone marrow from a megaloblastic to a normoblastic state, was observed. Further evidence that vitamin $B_{12}$ is inadequately absorbed in patients with pernicious anemia, reported by Berk *et al.* (67) and Hall *et al.* (78) is that vitamin $B_{12}$ orally administered to patients with pernicious anemia induced little or no hematopoietic activity, whereas the same or smaller doses swallowed simultaneously with normal gastric juice produced significant hematopoietic responses in the same patients. The greatest degree of response resulted from intramuscular administration of vitamin $B_{12}$, however. Berk *et al.* (67) suggest that extrinsic factor is closely related to, if not identical with vitamin $B_{12}$, and that the intrinsic factor in normal

gastric juice may be required for its absorption Spies *et al.* (79) have shown that oral doses of vitamin $B_{12}$ (administered without normal gastric juice) 30 to 50 times greater than the effective parenteral dose will produce hematopoietic responses in pernicious anemia, but conclude that parenteral administration is a more certain and effective mode of insuring proper therapy.

The question of the relative clinical merits of vitamin $B_{12}$ therapy and liver extract therapy in the treatment of pernicious anemia arises. In view of our present state of ignorance concerning the biochemical processes underlying hematopoiesis and with regard for the well-known fact that deficiency diseases tend to be multiple rather than single in character, it would seem wise to defer drawing any conclusions until ample evidence has been obtained demonstrating whether or not there are any other factors present in liver extract (80) besides vitamin $B_{12}$ which are beneficial to patients with pernicious anemia. On the other hand, the evidence (64) that liver extracts may contain an allergen absent in vitamin $B_{12}$ suggests that in individuals rendered allergic by liver extract, vitamin $B_{12}$ is the treatment of choice.

*Vitamin $B_{12}$ in nutritional macrocytic anemia.*—Early evidence (81, 82) indicated superiority of crude liver extracts to refined liver extracts in the treatment of nutritional macrocytic anemia. If one presumes that vitamin $B_{12}$ represents the antipernicious anemia factor responsible for the activity of refined liver extracts, one would not expect much of a therapeutic response in cases of nutritional macrocytic anemia to vitamin $B_{12}$. Spies *et al.* (71) have compared the effect of pteroylglutamic acid and vitamin $B_{12}$ in a case of nutritional macrocytic anemia and found them both to be effective. Subsequently, Spies and associates (68) found vitamin $B_{12}$ effective in four cases of nutritional macrocytic anemia with improvement in the red blood count and clinical symptoms. Patel (83) has reported the effectiveness of Smith's red crystalline compound (151) (vitamin $B_{12}$ produced in England) in two cases of tropical macrocytic anemia in India. It is too early to draw any conclusions from these early reports; more extensive clinical trials will undoubtedly clarify the status of vitamin $B_{12}$ in this syndrome.

*Vitamin $B_{12}$ in macrocytic anemia of pregnancy*—The relative efficacy of refined and crude liver extracts in the treatment of so-called pernicious anemia of pregnancy has been a controversial matter Watson & Castle (84) reviewed the literature on this subject prior to the widespread use of pteroylglutamic acid for this condition and presented evidence that oral liver extracts were more effective than parenteral liver extracts in two cases of macrocytic anemia of pregnancy. They concluded that their cases, at least, might be suffering from a deficiency of some nutrient other than that effective in Addisonian pernicious anemia, and suggested the term "Wills' factor" for the deficient substance. The effectiveness of pteroylglutamic acid in the treatment of macrocytic anemia of pregnancy has been clearly demonstrated, but it is worthwhile to point out that prior to the advent of vitamin $B_{12}$, Davidson *et al.* (85) reported three cases of "pernicious anemia of pregnancy" which responded well to pteroylglutamic acid after failing to improve

on liver extract therapy. In view of these findings, it is of great interest that Bethell *et al* (66) failed to produce either a clinical or hematologic remission in a young woman with puerperal macrocytic anemia with a dose of 1 µg. of vitamin $B_{12}$ intramuscularly daily for 10 days, whereupon 10 mg. of pteroylglutamic acid daily by mouth produced a good response hematologically with subsidence of glossitis.

Day and co-workers (86) have reported a case of a 27-year-old woman with macrocytic anemia of pregnancy (without evident dietary deficiency) with associated megaloblastic bone marrow, who was treated with parenteral liver extract without avail, then with 27.5 µg. of vitamin $B_{12}$ over an eight-day period with exacerbation of gastrointestinal symptoms, and finally with pteroylglutamic acid with prompt improvement manifested by clinical and hematopoietic remission. Although two case reports constitute but meager evidence and further confirmation is required, the evidence would tentatively suggest that this syndrome is a specific pteroylglutamic acid deficiency which will respond only to that nutrient or to substances in which it is contained.

*Vitamin $B_{12}$ in sprue*.—Spies *et al* (68) have reported the administration of vitamin $B_{12}$ to 11 cases of tropical sprue and one case of nontropical sprue, with striking clinical and hematologic improvement In an earlier report (87) Spies *et al.* suggested that combined liver therapy and vitamin $B_{12}$ might be superior to vitamin $B_{12}$ alone.

*Vitamin $B_{12}$ in the megaloblastic anemia of infancy*.—McPherson *et al.* (88) have recently reported the results of treatment of two infants suffering with megaloblastic anemia, with vitamin $B_{12}$ Both patients exhibited a good clinical and hematological response, although the dose required in one case was much higher than that in the other. Reisner (89), in a recent review of the current status of vitamin $B_{12}$, cites Luhby to the effect that vitamin $B_{12}$ is ineffective in the treatment of acute megaloblastic anemia of infancy. The relative values of vitamin $B_{12}$ and pteroylglutamic acid cannot be estimated until comparative studies have been performed.

*Other nutritional factors in hematopoiesis*.—Space limitations do not permit a discussion of the many other nutritional factors of proven or suspected importance in hematopoiesis. Such factors include protein, copper, iron, riboflavin, pyridoxine, nicotinic acid, pantothenic acid, *p*-aminobenzoic acid, pteroylglutamic acid, cobalt, and thymidine. Recent reviews have covered many of these nutrients (90 to 92).

In summary, it may be stated that. (*a*) though the cause of gastric mucosal atrophy in pernicious anemia is unknown, a deficiency in vitamin $B_{12}$ absorption may be a major factor in the pathogenesis of the signs and symptoms of that disease; (*b*) parenteral vitamin $B_{12}$ administration is an effective form of treatment for pernicious anemia, (*c*) vitamin $B_{12}$ has not yet been [illegible] number of cases of other forms of macrocytic anemia

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## POTASSIUM

*Potassium in nutrition.*—Although the potential toxicity of potassium administration in animals has been known for more than a century (93) and the association of potassium deficiency with the manifestations of familial periodic paralysis has been recognized for 50 years, it has been only recently shown that disturbances in the potassium economy are present in a wide variety of clinical states. Alteration in the level of the serum potassium with its attendant disturbances in the musculoskeletal system and in cardiac function have been described in nephritis, diabetic acidosis, intestinal obstruction, diarrhea, dehydration states, Cushing's syndrome, and Addison's disease. A better understanding of these potential disturbances in potassium metabolism should lead to more efficient utilization of parenteral fluid therapy.

Potassium is the chief cation of intracellular fluid. It is not permanently fixed in its intracellular location but may move about freely under certain circumstances, among which are alterations in acid-base balance, anabolism or catabolism of protoplasm, dehydration states, muscular activity, and phases in the cycle of carbohydrate metabolism. Although the serum content of potassium is small (5 m eq per l), fluctuations in this value may reflect profound disturbances in the total potassium content of the organism with associated objective criteria such as electrocardiographic abnormalities A normal serum potassium value, however, does not always indicate that the potassium balance is normal. Potassium is essential for deposition of glycogen and formation of protoplasm. The mode of excretion of potassium by the kidney is under considerable investigation at present.

*Familial periodic paralysis*—Danowski *et al.* (94) carefully studied two patients with familial periodic paralysis and concluded that attacks of paralysis are associated with a shift of extracellular potassium into the tissue cells with resulting drop in extracellular potassium concentration. Very little external loss of potassium occurs, save in the presence of considerable diuresis. Treatment with potassium chloride results first in deposition of potassium within the cells, and later in replenishment of the extracellular fluid potassium. Only when the latter has been achieved does the paralysis subside Gass *et al.* (95) reported a case of periodic paralysis (without family history of the disease) in which attacks of paralysis could be reproduced by ingestion of glucose The serum potassium fell with attacks of paralysis but there was no increased loss of potassium in stool or urine.

*Potassium and the electrocardiogram.*—Characteristic changes in the electrocardiogram in man associated with hypokalemia or hyperkalemia have been described by numerous investigators (96 to 99) With elevation of the serum potassium, the amplitude of the T wave increases, leading to "peaked" T waves, with subsequent decrease in the R wave and increase in S wave amplitudes P waves later disappear; RS-T segments are depressed, there is widening of the QRS, and the pulse rate falls (98). Reduction in the serum potassium may lead to depression of the T wave, depression of the ST segment, and prolongation of the P-R and Q-T intervals (99). Tarail

(99) described the relationship of the serum potassium level to the electrocardiogram in four patients with hyperkalemia. Electrocardiographic changes of hyperkalemia were rarely present below a serum level of 6 8 m.eq. per l, inconstant and variable between levels of 6 8 and 7.8, and always present above 7.8 m.eq. per l. The closest correlation in the serum-electrocardiogram change was always found within a given patient.

*Serum potassium levels and diabetic coma.*—There have been numerous recent reports confirming earlier observations (100) that potassium deficiency may occur during recovery from diabetic acidosis Martin & Wertman (101) found a marked fall in serum potassium levels occurring in nearly half of their patients with severe diabetic acidosis during treatment. The potential dangers of potassium (and magnesium) replacement therapy in these patients are emphasized; it is pointed out that patients in circulatory shock may be unable to excrete excess of the salts administered. Nicholson & Branning (102) felt that hypokalemia in diabetic acidosis may result from loss of intracellular potassium by diuresis and dehydration, depletion of serum potassium as a result of insulin therapy, and reduction in serum concentration as a result of hemodilution brought about by parenteral fluid therapy (in the absence of potassium intake). Frenkel *et al* (103) emphasize the respiratory difficulty ("fishmouth" breathing), generalized muscular weakness, and cardiac abnormalities which led them to suspect correctly the syndrome of hypokalemia in a patient recovering from diabetic coma. The patient promptly recovered when given oral potassium salts. Tuynman & Wilhelm (104) report a similar experience in which respiratory difficulty and muscular weakness accompanied the hypokalemia; recovery following potassium therapy ensued. Nadler *et al.* (105) point out that a normal or high initial serum potassium level in diabetic acidosis does not preclude a low total body potassium concentration, and that the serum potassium drops most rapidly between the third to eighteenth hour after insulin therapy. Danowski *et al.* (106), as a result of balance studies in eight patients, reported evidence that intracellular potassium is depleted during diabetic acidosis, by demonstrating retention of administered potassium beyond amounts calculated necessary for deposition of cell protein. A more recent report (107) from the same laboratory indicates that the contributory factors to the development of hypokalemia during the early stages of recovery from diabetic acidosis are (*a*) dilution of extracellular fluid by parenteral fluid administration; (*b*) urinary potassium loss; (*c*) migration of potassium into cells with deposition of glycogen and protein

Sinden, Tullis & Root (108) advise avoidance of intravenous glucose and institution of early feeding by mouth of orange juice and other potassium rich foods in addition to insulin therapy as practical measures in the prevention and treatment of hypokalemia during diabetic coma. Stephens has recently reported a case (109) of diabetic acidosis that required 33 gm of potassium chloride before hypokalemia could be permanently corrected The patient had considerable gastric retention and could not be fed by mouth

during the early stages of recovery. The author points out that administration of glucose during the treatment of diabetic acidosis may be a contributory factor in the development of hypokalemia.

In their extensive studies, Guest & Rapoport (110) have laid stress on the loss of organic acid-soluble phosphorus concomitant with loss of potassium from red blood corpuscles in diabetic acidosis; these observations have been confirmed by others (111).

*Potassium deficiency in diarrhea.*—Darrow (112) has demonstrated the loss of considerable quantities of intracellular potassium in infantile diarrhea. Govan & Darrow (113) have been able to reduce the mortality of this condition considerably by the use of solutions containing potassium chloride. Details of the treatment are presented and such precautions as the administration of glucose or saline prior to potassium chloride therapy in order to insure adequate diuresis are discussed. Potassium intoxication (114) may occur unless these precautions are observed. A recent review by Darrow, dealing with the therapy of diarrhea and other conditions associated with electrolyte disturbance has appeared (115).

*Disturbance in serum potassium associated with chronic nephritis.*—A number of reports have appeared relating renal impairment with disturbances in serum potassium levels. Finch *et al.* (116) point out that average normal intake of potassium is 3 4 gm. per day with 80 per cent urinary and 20 per cent fecal excretion; and that in severe renal insufficiency, potassium excretion may be diminished, although most patients with uremia have normal serum levels. The lethal blood level is said to be about 10 to 10.5 m.eq per l. however, one patient with a level of 12.2 m.eq per l has recovered upon prompt recognition of the condition (114). Finch *et al.* (116) report two cases of potassium intoxication associated with paralysis and typical electrocardiographic changes associated with renal insufficiency An interesting observation is that tissue trauma, as in the crush syndrome or hemolytic reactions, may release large amounts of potassium because of the high potassium content of tissue cells and red blood corpuscles The differential diagnosis of paralytic symptoms is discussed, and mention is made of the fact that chronic nephritis with a low serum potassium may also be associated with paralysis. Langendorf & Pirani (117) found electrocardiographic evidence of hyperkalemia present in six of a series of 27 patients with clinical uremia. Keith & Osterberg (118) noted a varied incidence of paresthesias, decreased renal potassium excretion, and rise in serum potassium in several patients with severe renal insufficiency to each of whom a dose of 5 gm. of potassium bicarbonate had been administered. One patient's electrocardiogram revealed evidence of intraventricular block. Keith & Burchell (119) reported thirteen cases of hyperpotassemia associated with uremia, all of whom died Characteristic clinical signs were not present in this group. Mild degrees of renal impairment may also be associated with potassium intoxication, with accompanying electrocardiographic changes in the experience of Stewart and his associates (98). Perfusion of the bowel was effective in

lowering the serum potassium and relieving the paralytic symptoms in a case of hyperkalemia associated with chronic nephritis reported by Nicholson & Spaeth (120). The treatment did not prevent the patient's death a few weeks later, at which time the serum potassium was within normal limits. Elkinton *et al.* (121) concluded from a study of 26 patients with uremia, half of whom had hyperkalemia, that the principal disturbance in potassium excretion was a decreased glomerular filtration rate. Reports have appeared demonstrating the effectiveness of the artificial kidney in reducing serum potassium levels in hyperpotassemia due to uremia (122, 123).

In some cases of renal dysfunction, the signs and symptoms of potassium deficiency rather than intoxication may prevail; and although the symptoms may be very much alike in the two conditions, the electrocardiogram serves as a considerable aid in differentiation. Brown and co-workers (124) found electrocardiographic changes typical of hypokalemia in three patients with chronic renal disease and flaccid paralysis. Treatment with potassium citrate resulted in return to normal muscle function and electrocardiographic patterns. The authors discuss a possible relationship between digitalis overdosage and low cardiac muscle potassium in the production of abnormal cardiac impulses. Others have also observed hypokalemia in renal insufficiency (121).

*Miscellaneous conditions with disturbance of serum potassium levels.*— Bellet *et al.* (125) conducted a noteworthy study of 15 patients with intestinal obstruction, in all of whom the initial serum potassium was low. Parenteral fluid therapy without potassium resulted in lower serum potassium levels. Electrocardiographic evidences of hypokalemia were noted in all patients to be reversible upon intravenous potassium administration, in proportion to the dose given. Prior calcium administration to several of the patients was without effect. The severity of the hypokalemia seemed related to the degree of alkalosis. Pathogenesis, diagnosis, and treatment of this syndrome are discussed. Kennedy *et al* (126) reported a case similar to those of Bellet, occurring postoperatively, manifested by apathy, drowsiness, and evidence of alkalosis, responding to treatment with potassium chloride and ammonium chloride. Alkalosis and hypokalemia as a result of persistent vomiting have been reported in infants with exacerbation of the hypokalemia during saline and glucose therapy (127). Nicholson & Spaeth (120) reported the occurrence of hyperkalemia following administration of potassium salts to an apparently unsuspected case of Addison's disease Recovery followed upon institution of endocrine therapy for Addisonian crisis. A case of sprue with symptoms associated with hypokalemia relieved by intravenous potassium chloride is reported in the same communication.

Engel and co-workers (128, 129) have presented evidence indicating that the concomitant low serum potassium levels in two cases of chronic diarrhea with hypocalcemia served to prevent the manifestations of tetany. Alkalosis, hypochloremia, and hypokalemia have been reported (130) occurring in 15 patients maintained on intravenous feeding following major surgical pro-

cedures. The clinical and electrocardiographic manifestations which occurred were reversed by potassium therapy.

*Studies of potassium economy.*—Since the demonstration that sodium and potassium ions traverse cell membranes under certain conditions, considerable investigation of the behavior of these ions in altered metabolic states has taken place. Elkinton & Winkler (131) obtained data in dogs suggesting that dehydration resulted in a loss of intracellular water along with loss of intracellular potassium, with a consequent minimizing of loss in extracellular water. The intracellular potassium deficit was calculated to be in excess of that excreted as a result of protein catabolism, and renal activity was found necessary to effect the potassium loss. Darrow and associates (132) were able to find a high degree of inverse correlation between levels of serum bicarbonate and muscle potassium, and direct correlation between serum bicarbonate and intracellular sodium in rats subjected to various procedures resulting in depletion of sodium, potassium, or chloride. The authors point out that these correlations obtain only in the presence of adequate renal function and adjustment to the altered ionic states and do not hold in "unstable" states such as diarrhea or dehydration Folk and co-workers (133) have found potassium concentrations of interstitial fluid in a variety of patients suffering with edema or transudates to be almost equivalent to serum potassium concentrations. The migration of sodium into the cell in potassium depleted states as a simple replacement measure has been questioned Elkinton *et al* (134) found that although sodium does enter the cell under certain circumstances in which intracellular potassium has been diminished, this is not an invariable consequence, nor are the exchanges of equivalent magnitude. A direct approach to the problem of determining intracellular sodium and potassium shift in acidosis and alkalosis has been reported by Mudge & Vislocky (135). These investigators analyzed muscle biopsies of patients with acidosis due to chronic nephritis and also of patients with alkalosis due to vomiting The concentration of intracellular potassium was decreased, and that of sodium increased in both the cases of alkalosis as well as those of acidosis. Their findings suggest that the over-all negative potassium balance rather than the acid-base balance was the determining factor in the changes found. Tarail & Elkinton (136) observed retention of administered potassium in patients deprived of potassium by intestinal disorders, and they further observed that urinary potassium excretion decreased during the period of therapy with potassium salts. Mateer and co-workers (137) point out earlier evidence indicating that in food and water deprivation states, urinary sodium excretion falls to zero, whereas potassium urinary excretion continues, and that the latter results in intracellular potassium depletion, unless there is renal suppression, suggesting that the kidney is incapable of conserving potassium in the face of potassium depletion. However, studies by these authors and others (138) would indicate that this is not necessarily true, and that renal conservation of potassium may occur under certain circumstances. Evidence obtained from experiments in dogs

(139, 140) indicates the existence of a tubular excretory (secretory) mechanism for potassium. Mercurial diuretics have been found to diminish the excretion of potassium under certain circumstances, and it has been suggested that the action of the mercurial is exerted on this tubular secretory mechanism (141). Gastrointestinal motility of rats rendered deficient in potassium has been shown to be depressed (142).

In summary it may be pointed out that disturbances in potassium content of the body with potentially adverse effects on cardiac, respiratory, and voluntary muscle function may supervene in states of altered metabolism and nutrition, dehydration, renal insufficiency, and probably overhydration, and that previous concepts of parenteral and oral replacement therapy of electrolytes are being modified

## Parenteral Alimentation

Parenteral nutrition is necessary whenever the gastrointestinal tract cannot or should not be used, either completely or partially. Such states accompany a variety of medical and surgical conditions. Parenteral nutrition at present is limited largely to the administration of glucose, saline, blood, protein, hydrolysates, and water-soluble vitamins. The degree of completeness of parenteral nutrition depends on the nutritional status of the individual patient and the length of time over which parenteral nutrition is needed. The principal inadequacy of complete parenteral nutrition when it is needed in an emaciated patient, or for prolonged periods, is the inability to provide sufficient calories in a reasonable fluid volume. To overcome this lack, attempts have been made to prepare finely divided emulsions of fat that can be given intravenously

Stare and his associates have been working on this problem for the last several years. In a series of experiments on animals (143 to 146), they have shown that suitable fat emulsions given intravenously are utilized for energy purposes Absolute proof for the utilization of fat emulsions was obtained by incorporating radiocarbon into the fat molecule and showing that it could be detected rapidly, and in large amounts, in the expired carbon dioxide (147).

Two recent papers by Stare and his colleagues report in some detail the use of fat emulsions in man (148, 149). A total of 17 patients were studied. These included 14 adults, two children, and one infant. The emulsion used consisted of 15 per cent coconut oil, 4 3 per cent dextrose, stabilizer, and water. It furnished 1,600 kcal. per l and was given at rates ordinarily used for administering glucose or saline solutions. Amounts up to 5 gm of fat per kg. of body weight were given to adults and 6 gm. of fat per kg. of body weight to a seven-week infant Infusion periods ranged from 3 to 27 consecutive days. The emulsion was effective as indicated by favorable clinical response, prevention of weight loss, and maintenance of positive nitrogen and potassium balance. Subsequent post-mortem examination of six of these

patients revealed that the fat emulsions had produced no pathological change, either gross or microscopic.

The fat emulsion used is not considered completely satisfactory from the clinical viewpoint because it tends to develop pyrogenicity after it is approximately four weeks old. However, the fact that fat emulsions suitable for parenteral use in man can be prepared, and that such fat given intravenously is utilized, gives promise of furnishing the major deficit in present-day parenteral nutrition, namely, adequate calories in a reasonable fluid volume.

Shafiroff and colleagues (150) have reported on the use in patients of a 10 per cent fat emulsion combined with 5 per cent protein hydrolysate, 5 per cent glucose, and using gelatin at 2 per cent as the emulsifying agent. The caloric value of this emulsion is about 1,300 per l. They have given such an emulsion intravenously to 76 patients and state that a variety of laboratory and clinical observations provide evidence of its suitability as an intravenous emulsion.

## Conclusion

Modern nutrition deals with the relations of some 50 to 60 nutrients to cellular growth and metabolism. In the absence of a proper supply of nutrients, cells cease to function and die. Thus, nutrition is of major importance in health and in all phases of medicine. As stated in the introduction to this chapter, in present day America, nutrition is the single most important environmental factor affecting health, and hence an understanding of modern nutrition is of the greatest importance in the practice of medicine In this review some of the nutritional measures employed in the treatment of hypertension have been discussed as well as recent findings concerning vitamin $B_{12}$ and potassium that are of importance to medicine. Brief mention has been made of the potentialities of using fat emulsions as a part of parenteral nutrition in order to supply adequate calories in a limited fluid volume—a development that has considerable promise in the treatment of any condition accompanied by emaciation.

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# ALLERGY

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This is an era of chemotherapy. For the allergist one might even say that this is a reign of antihistaminics. Studies on the antihistaminic substances have occupied the time and energy of investigators interested in manifestations of hypersensitivity to the extent that their writings have dominated the medical literature during the past few years. The summit of interest in and research on these compounds has most surely been reached. It is fitting, therefore, that this chapter in this first volume be devoted for the most part to a discussion of these drugs. To maintain unity of thought the remaining portion of the chapter will be concerned with other therapeutic advances and with allergic reactions to drugs and chemical compounds.

## Histamine and the Antihistaminic Drugs

In the anaphylactic body, the only tissues which, according to present evidence, are directly responsive to the antigen-antibody reaction are involuntary muscle, capillary endothelium and possibly certain glandular cells. The tissues affected by histamine and anaphylactic reactions are identical, and naturally it has been assumed that the tissue response from the antigen-antibody reaction is due to a release of histamine or a histamine-like substance.

Epinephrine favorably combats the anaphylactic reaction. Furthermore, epinephrine and histamine act on effector cells in opposite directions and the action of one tends to neutralize the action of the other. Epinephrine, therefore, is an effective antihistaminic substance, and this type of antihistaminic action is spoken of by the pharmacologist as physiologic antagonism. This physiologic antagonism between epinephrine and histamine may be at play within the body constantly as a compensatory mechanism. To lend support to such a theory is the recent evidence that the intravenous administration of epinephrine or synephrine provokes a significant increase in the histamine blood level. The percentage of rise in the histamine blood level in allergic and normal individuals following the intravenous injection of 0.2 mg of epinephrine is similar, though the resting histamine blood level in allergic patients is frequently higher (160 µg per l.) than that found in normal controls (60 to 80 µg. per l.) (1 to 4).

An exemplification of the extent to which eccentricity may accompany scientific endeavors is the evidence of an increase in the histamine blood level following an injection of either Antergan, Neoantergan or Phenergan (5) To explain this aberration from logical expectancy Pellerat (5) conceived the theory that tissue histamine is displaced by antihistaminic substances and liberated into the blood stream. The acceptance of Pellerat's data must await confirmation by other investigators.

*Another facet to the inspiring theory of the compensatory* mechanism between histamine and epinephrine has lately been added. Fatal pulmonary edema in rabbits and guinea pigs following intravenous epinephrine can be prevented by pre-treatment with antihistaminic susbtances. The explanation ventured is that pulmonary edema from epinephrine is the sequela of histamine release (6, 7).

Recently (8) it has been proposed that "epinephrine-fastness," may be partially due to the release of histamine by epinephrine. In other words, the successive administration of epinephrine to an epinephrine-refractory asthmatic patient might act to aggravate the condition by inciting the additional and repeated release of histamine.

The pharmacological effects of histamine are due to its action upon the glands of external secretion as well as upon the peripheral blood vessels and involuntary muscles. Histamine acts as a secretogogue for the nasal, lacrimal, pulmonary and digestive glands of external secretion By coupling the knowledge of the action of histamine on the nasal glands with the evidence that certain vasoconstricting agents actuate the release of histamine upon introduction into the body, it has been suggested (9) that the unfavorable reaction in the nasal mucous membranes of patients following the indiscriminate usage of vasoconstrictor solutions might be due to the local release of histamine. *To test out the veracity of such a theory nasal solutions, containing* (*a*) Privine 0.05 per cent and Pyribenzamine 0.5 per cent and (*b*) Privine 0.05 per cent and Antistine 0.5 per cent, were given to patients with allergic rhinitis No unfavorable reactions from Privine were encountered and some patients who could not tolerate Privine alone tolerated the Privine-Antistine and the Privine-Pyribenzamine solutions with impunity (9).

Ephinephrine and related vasoconstrictor drugs, therefore, inasmuch as they act in antagonism to histamine, are well defined as antihistaminics. However, are we justified in speaking of Benadryl, Pyribenzamine, Histadyl, Neoantergan, etc., as antihistaminics? It was at first thought that these drugs blocked rather than antagonized the action of histamine, in other words, a mechanism of action similar to that by which atropine blocks the effects of acetylcholine. Accordingly, Gilman (10) suggested that the term histaminolytic would be more applicable than the term, antihistaminic. At that time effect of these drugs upon the capillary bed had not been adequately studied Very recently Haley & Harris (11) have demonstrated that Benadryl, Decapryn, Diatrin, Tagathen, Histadyl, Neoantergan, Neohetramine, Antistine, Phenergan, Trimeton and Thephorin have a vasoconstrictor action on the precapillary sphincters of the mammalian capillary bed Histamine has a vasodilator action upon the precapillary sphincters Furthermore, epinephrine and the antihistaminics cause the leucocytes to adhere to the vessel walls while histamine makes the cell wall and/or the leucocytes less adherent. Therefore, the antihistaminic drugs and histamine act upon the same effector cells in opposite directions and compete for the same site of

action. The antihistaminics, like epinephrine and related vasoconstrictor drugs, are well defined as antihistaminics.

The vasoconstrictor effect produced by the antihistaminics upon the capillary bed explains the decrease in the extravasation of dye in the skin of rabbits and dogs after the intradermal injection of histamine (12 to 22), the decrease of the wheal and flare that occurs in man after the intradermal injection of histamine (23), the reduction of the tuberculin skin reaction (24, 25), and the decrement of the egg white type of edema in rats (26, 27).

The action of Dramamine, which is an 8-chlorotheophyllin salt of Diphenhydramine, upon the mammalian capillary bed is not similar to that of the antihistaminics. Dramamine acts as a vasodilator and its effect is not upon the precapillary sphincters but upon the arterioles Undoubtedly the vasodilator effect of this drug is due to the 8-chlorotheophyllin part of the molecule and the fact that its action is more potent than the Diphenhydramine portion (11).

Within the past three years the medical literature has been studded with reports on antihistaminic substances. Because of the great and unfortunate variety of techniques used in studying these compounds it has become increasingly difficult and hazardous to interpret, analyse, compare and evaluate the data submitted. Particularly treacherous is the evaluation of clinical observations where the personality equations of the investigator and the patient are so variable Then, too, the very nature of the allergic condition makes for difficulty in the appraisal of any therapeutic agent.

For the sake of clarity, accuracy, and simplicity the data analysed in this section of the review will be presented under the following headings: chemistry; *in vitro* experiments employing the Dale technique; histamine intoxication; animal anaphylaxis, clinical observations; and side effects.

*Chemistry.*—Upon scrutiny of the chemical structures of the numerous antihistaminic substances, certain similarities common to the most potent ones, become apparent Many can be segregated into two groups dependent

TABLE I

Compounds with ETHANOLAMINE as a Basic Unit

| Name | Formula |
|---|---|
| BENADRYL<br>$\beta$-dimethylaminoethyl-benzhydryl ether | HCO $CH_2 \cdot CH_2 \cdot N(CH_3)_2$ |
| DECAPRYN<br>Dimethylaminoethoxy-methylbenzylpyridine | $CH_3$ CO $CH_2 \cdot CH_2$ $N(CH_3)_2$<br>N |

TABLE II.

Compounds with ETHYLENEDIAMINE as a Basic Unit

| Name | Formula |
|---|---|
| PYRIBENZAMINE<br>N'-pyridyl-N'-benzyl-N-dimethylethylenediamine | $CH_2$<br>N<br>$N\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$ |
| HISTADYL or THENYLENE<br>N'-pyridyl-N'-thenyl-N-dimethylethylenediamine | S<br>$CH_2$<br>N<br>$N\cdot CH_2\ CH_2\cdot N(CH_3)_2$ |
| ANTERGAN<br>N'-phenyl-N'-benzyl-N-dimethylethylenediamine | $CH_2$<br>$N\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$ |
| NEOANTERGAN<br>N'-p-methoxybenzyl-N'-pyridyl-N-dimethylethylenediamine | $CH_3O$<br>$CH_2$<br>N<br>$N\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$ |
| HETRAMINE<br>N'-benzyl-N'-2-pyrimidyl-N-dimethylethylenediamine | $CH_2$<br>N<br>N<br>$N\cdot CH_2\cdot CH_2\ N(CH_3)_2$ |
| NEOHETRAMINE<br>N'-p-methoxylbenzyl-N'-2-pyrimidyl-N-dimethylethylenediamine | $CH_3O$<br>$CH_2$<br>N<br>N<br>$N\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$ |
| BROMOTHEN<br>N'-pyridyl-N'-5-bromo-thenyl-N-dimethylethylenediamine | Br—S<br>$CH_2$<br>N<br>$N\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$ |
| CHLOROTHEN<br>N'-pyridyl-N'-5-chloro-thenyl-N-dimethylethylenediamine | Cl—S<br>$CH_2$<br>N<br>$N\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$ |

TABLE III

Miscellaneous Compounds

| Name | Formula |
|---|---|
| ANTISTINE<br>N'-phenyl-N'-benzylamino-methylimidazoline | $CH_2$; N $CH_2 \cdot C$; N, $CH_2$, N H, $CH_2$ |
| THEPHORIN<br>2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene | $CH_3$; N |
| PHENERGAN<br>N-dimethylamino-iso-propylthiodiphenylamine | S; $N \cdot CH \cdot CH_2 \cdot N(CH_3)_2$; $CH_3$ |
| TRIMETON<br>2-pyridyl-$\beta$-N,N-dimethyl-amino-ethylmethane | $HC \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$; N |
| CHLOR-TRIMETON<br>1-(p-chlorophenyl)-1-(2-pyridyl)-3-n,N-dimethylpropylamine | Cl; $HC \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$; N |
| PERAZIL<br>N-methyl-N'-(4-chloro-benzhydryl)-piperazine | Cl; $HC \cdot N$; $H_2$ $H_2$, C C; $N \cdot CH_3$; C C, $H_2$ $H_2$ |
| PYRROLAZOTE<br>$\beta$-pyrrolidine-ethyl-phenothiazine | S; N $CH_2 \cdot CH_2 \cdot N$; $H_2$ $H_2$, C C; C C, $H_2$ $H_2$; HCl |

upon the existence in the molecule of the basic unit, ethanolamine [Benadryl, Decapryn (TABLE I)] or the basic unit ethylenediamine [Pyribenzamine, Histadyl, Neoantergan, Antergan, Bromothen, Chlorothen, Neohetramine (TABLE II)]. Common to these two groups is a terminal nitrogen atom which is a tertiary amine and this component of the structure contributes favorably to the potency of the entire molecule (23). Dimethylamine instead of diethylamine groupings on the tertiary amine makes the compounds less toxic The distance between the oxygen and nitrogen (TABLE I) or the two nitrogen atoms (TABLE II) of the side chain is equal to not more than two carbon atoms. Increased length and branching detracts from activity. Certain alterations of the aromatic nuclei attached to the alpha nitrogen atom can be made without interfering with activity A displacement of the pyridyl (Pyribenzamine, Neoantergan, Histadyl, Bromothen, Chlorothen) with the pyrimidyl group (Hetramine, Neohetramine) does not interfere appreciably with potency. The addition of a para-methoxy group to the benzyl nucleus enhances activity (Neoantergan versus Antergan; Neohetramine versus Hetramine). The substitution of a thenyl (Diatrin, Histadyl, Thenylene, Methapyrilene) or halogenated thenyl group (Bromothen, Chlorothen, Tagathen) for the benzyl or pyridyl group decreases the vasoconstrictor potency (11)

The structural formulae of the remaining compounds (TABLE III) vary in different degrees from the two large groups of compounds already discussed. There is great similarity in structure between Trimeton and Pyribenzamine and Benadryl but in Trimeton a methane grouping has been substituted for the oxygen atom of Benadryl and the alpha N atom of Pyribenzamine. Trimeton further varies from Benadryl in that the former has a pyridyl group in place of the phenyl group of Benadryl. In Antistine the terminal N atom has become a part of a heterocylic group and this cyclization of the terminal amine group does not have any effect on the potency of the compound as measured on the capillary bed. Phenergan and Pyrrolazote are both thiodiphenylamine derivatives. Perazil and Thephorin, especially the latter, are very dissimilar in structure to all other compounds. All of these antihistaminics, regardless of structure, possess clinical activity of a comparable degree as will be pointed out later in this discussion.

*Experiments in vitro, Dale technique.*—Ineluctable deceptions and unavoidable inaccuracies accrue from experiments with the Dale technique because of the erratic behavior of the isolated intestine (28, 29). Because of this and the slight variations in technique employed by different investigators special precautions and meticulous care must be exercised in evaluating small differences in effectiveness of compounds tested

By exercising conservatism, even despite the hazards offered by this technique, certain conclusions can be drawn. Histadyl (29, 30), Chlorothen (29, 31), Bromothen (29, 31), Pyribenzamine (29) and Neoantergan (29, 32, 33) are more potent than Phenergan (29, 34) and Benadryl (29, 32, 35); Antistine (29, 35) is the least potent of all.

*Histamine intoxication.*—Three methods have been used to study the

histamine blocking effect of antihistaminics in the intact guinea pig: (*a*) the injection of a fixed dose of antihistamine substance prior to the intravenous administration of histamine and thereby ascertaining the number of lethal doses of histamine that can be tolerated (36, 37); (*b*) the administration of antihistaminics by injection or by mouth and noting the protection against histamine aerosol (33, 37, 38); and (*c*) the determination of the smallest amount of antihistamine substances that will afford protection against one lethal dose of histamine injected intravenously (33), intracardially (39) or intraperitoneally (40, 41).

Slight differences in the comparative effectiveness of the various antihistaminics, because of the diversity of methods and procedures, are insignificant. However, it is noteworthy that whenever Neoantergan has been compared with other antihistaminics, regardless of the technique employed for testing, it has always proven to be the most effective (33, 35, 39). Pyribenzamine (31, 33, 39), Histadyl (29, 41), Bromothen (39), Chlorothen (39), Benadryl (33, 35, 39, 41), Phenergan (39), Hetramine (33), and Antistine (35, 39) are usually rated in regard to comparative potency in the order given.

There is, therefore, a remarkable conformity in regard to the order of potency of the various antihistaminic compounds as determined by the Dale technique and by the *in vivo* experiments in the intact guinea pig when testing for activity against histamine intoxication

*Animal anaphylaxis.*—Guinea pigs have been employed by most investigators for anaphylaxis experiments, and a great variety of foreign proteins have been used as sensitizing antigens The usual procedure has been to administer the sensitizing dose of antigen, to wait 14 to 21 days for hypersensitivity to develop, to administer the antihistaminic substance, and then within 10 to 60 minutes thereafter to give the challenging dose of antigen. By this method of investigation, Neoantergan (39, 40), Antergan (40), Pyribenzamine (39, 40, 42, 43, 44), Histadyl (39), Bromothen (39), Chlorothen (39), Thephorin (45), Neohetramine (44), Benadryl (39, 40, 43, 46), Hetramine (47), Phenergan (34, 39), Antistine (39), Diatrin (48), and Pyrrolazote (49) have been shown to be potent Very few authors have studied the comparative effectiveness of many different compounds However, Landau *et al.* (39), studying 9 compounds, found that the protective doses of Neoantergan, Pyribenzamine, Histadyl, Bromothen, Chlorothen, Benadryl, 1721 (Searle), and Phenergan were almost equal, and that larger doses of Antistine were required to confer upon animals a similar degree of protection Rose *et al.* (40) reported that Neoantergan, Pyribenzamine, Antergan and Benadryl were equivalent in protective power.

Protection against anaphylactic shock requires much higher doses of antihistaminics than for protection against histamine intoxication (39) Because of this discrepancy it is not necessary to imply that anaphylaxis in the guinea pig is not the result of histamine release It is probable that there is intracellular release of histamine as a result of antigen-antibody reaction (10) The opportunity for effectiveness of an antagonizing substance is less be-

cause of this than if the histamine came to the cells by way of the blood stream. It is, therefore, intelligible why reactions to histamine which depend upon diffusion of histamine into tissues from the blood stream can be more competently antagonized by antihistaminics than those reactions which result from release of histamine directly within the effector cells.

## Clinical Observations on Antihistaminic Drugs

*General.*—There are few data available on the stability of antihistaminic substances. Trimeton discolors slowly on exposure to sunlight and interacts with rubber (50). Landau & Gay (29) reported that Phenergan had oxidized en route from France to their laboratories and that the potency of high dilutions of several drugs decreased even though they were refrigerated They did not enumerate the drugs so affected.

The modicum of data on absorption and excretion is regrettable. Following the administration of 400 mg. of Benadryl in 50 cc. of water by mouth under fasting conditions, the concentration of Benadryl in the blood reached a peak of 1.07 μg. per cc. within a period of 90 to 120 min. Under similar circumstances Pyribenzamine attained a peak concentration of only 0 4 μg. per cc. after 180 min. Twenty-four hours after 400 mg. of Benadryl and Pyribenzamine were administered orally, 46 per cent and 20 per cent respectively had been excreted in the urine (51).

Benadryl administered orally in therapeutic doses has no effect on the body temperature, the basal metabolic rate, the body weight, the pulse rate, the blood morphology, the electrocardiogram, and the glucose tolerance curves (52 to 54). There may be a decrease in the blood pressure which persists for 1 to 2 hours following the oral administration of 50 to 100 mg. (55) However, following the intravenous administration of either 200 mg or 300 mg. of Benadryl in 50 cc of distilled water the systolic and diastolic blood pressures rise on an average of 30 to 40 mm. and 20 to 30 mm. respectively. The pulse rate also increases 20 to 25 beats per minute This cardiovascular reaction persists for about 60 minutes and then begins to subside (56)

Pyribenzamine given orally in doses of 150 mg. a day has no effect on body weight, blood pressure, urine, blood urea nitrogen, liver function, and blood morphology (57).

Neohetramine (58) in daily doses of 200 to 400 mg. and Thephorin (59) in a daily dose of 300 mg by mouth do not affect the blood morphology, the urine, the blood pressure, and the electrocardiogram of normal individuals. Inversion of the T waves in Lead $CV_4$ in patients with arteriosclerotic heart disease have been observed following the oral administration of 300 mg. of Thephorin. The changes disappeared after withdrawal of the drug (59).

Electroencephalograms following the administration of 200 mg doses of either Benadryl, Pyribenzamine, Neohetramine, or Thephorin show identical changes of fast activity superimposed on a normal alpha rhythm. There may also be a decrease in the amplitude of the waves (59).

*Seasonal and perennial allergic rhinitis.*—The therapeutic effectiveness

of antihistaminic drugs is not modified by the type of antigen setting off the hypersensitive reaction in the nose. The symptoms of sneezing, rhinorrhea, lacrimation, and itching of the eyes and nose are more favorably relieved than nasal congestion (60). Pyribenzamine (60 to 65), Hydryllin (60, 64), Antistine (60, 64, 66, 67), Neoantergan (60, 61, 64, 65, 67, 68), Histadyl (41, 60, 69, 70), Benadryl (60, 61, 63, 71), Thephorin (59, 72), Neohetramine (58, 64, 67, 73), Chlorothen (60), Decapryn (74, 75) and Trimeton (67, 76, 77) give beneficial results in from 60 to 80 per cent of the patients treated. The degree of relief depends upon the dosage employed and the patient's tolerance of the drug. Although Pyribenzamine, when it has been compared with other substances, has proved to be superior in effectiveness (60, 61, 62, 64), this difference is not great, and it is imperative to stress that any one compound is not generally superior to all others, It is not an uncommon experience to find patients who will benefit from one drug but not another, so that if symptomatic relief is not forthcoming during treatment with a particular antihistaminic substance, other compounds should be given a trial.

The oral dose for all compounds, excluding Chlor-Trimeton, is similar. At the onset of treatment a small dose (25 to 50 mg.) administered regularly after each meal and at bedtime, or periodically as necessary to relieve symptoms, is advisable. The dose may be increased until relief is obtained or until side effects are experienced Amounts of Antistine (60) and Neohetramine (73) larger than of other antihistaminics are necessary to provide comparable relief. Because Chlor-Trimeton is more stable and its destruction in the body more delayed than that of other antihistaminic substances, the dose for this compound is distinctly smaller (2 to 4 mg ).

The topical application of two to three drops of a 0.5 per cent solution of Pyribenzamine in the nose every three to four hours gives symptomatic relief and reduces the engorgement of the inferior turbinates The duration of relief varies from one to twenty-four hours depending upon the severity of the symptoms. Local reactions such as burning in the nose and pharynx and sneezing occur, but general reactions have not been reported (78, 79). The unpleasant local reactions following the use of the nose drops are partially mitigated by employing the solution as a spray (79). The instillation into the conjunctival sac of one to two drops of a 0 5 per cent solution of Antistine (66) or a solution combining 0 5 per cent Antistine and 0 025 per cent Privine (80) is often effective in relieving the burning, itching, photophobia and lacrimation caused by allergic reactions in the conjunctivae.

The gratifying symptomatic relief afforded by the antihistaminic compounds must not divert or detract interest in the search for etiological factors and must not encourage the withholding and exclusion of specific desensitization therapy Desensitization with specific antigens, as a therapeutic measure by itself, is superior to symptomatic treatment with antihistaminic drugs. Furthermore, asthma is likely to develop in patients with allergic rhinitis during treatment with only antihistaminic substances, whereas asthma rarely occurs in patients receiving perennial or preseasonal desensitization therapy.

Desensitization and antihistaminic substances employed together provide the optimal opportunities for efficacious results (65).

*Bronchial asthma*.—Critical investigators have called attention to the poor results obtained in the treatment of bronchial asthma. About 25 to 50 per cent of the patients treated with Pyribenzamine (60 to 64), Hydryllin (60, 64), Antistine (60, 66), Neoantergan (60, 61, 64, 68), Histadyl (60), Benadryl (61, 63, 71), Thephorin (59), Neohetramine (58), Decapryn (74, 75), and Trimeton (76, 77) are benefited. In a few instances where the effectiveness of several compounds has been compared, Hydryllin (60, 64) and Neoantergan (60) have met with the most success. But in the treatment of asthma, as in the treatment of allergic rhinitis, the differences in effectiveness of the various drugs are not of sufficient degree to merit dogmatism. Only patients with non-infective bronchial asthma presenting very mild symptoms are benefited. Patients with infective bronchial asthma are not affected favorably and, as a matter of fact, it is probably not wise to attempt treatment of such patients with the antihistaminic compounds because of their drying effect.

*Urticaria and angioneurotic edema*.—The antihistaminic drugs attain their zenith of effectiveness in acute urticaria and angioneurotic edema. Pyribenzamine (60 to 63, 81, 82, 83), Antistine (60, 66, 84), Benadryl (61, 63, 71, 81, 82, 83), Histadyl (60, 82), Neoantergan (60, 85), Hydryllin (60, 86), Neohetramine (58, 73), Thephorin (59), Decapryn (74), and Trimeton (76) are of comparable efficacy. From 60 to 90 per cent of patients treated receive varying degrees of subjective and objective relief despite the compound employed. Pruritus is usually the first clinical manifestation to be ameliorated, followed by an alleviation of erythema and edema. Pruritus may be promptly abated by the intravenous administration of from 20 to 50 mg. of Benadryl in 75 to 100 cc. of isotonic sodium chloride solution and this mitigation usually persists four to eight hours (71). The author has procured more satisfactory and durable palliation by administering 100 mg. of Benadryl or 200 mg. of Histadyl in 250 cc. of isotonic sodium chloride solution over a period of one to three hours and repeating the procedure as necessary throughout a 24 hour period. At the present time only Benadryl and Histadyl are commercially available in solutions for parenteral injection. Chronic urticaria and angioneurotic edema respond less dramatically to antihistamine therapy than the acute forms.

*Pruritic dermatosis other than urticaria and angioneurotic edema*.—The antihistaminic drugs do not alter the course of any skin disease other than by the indirect effect of reducing trauma through the amelioration of pruritus. An appraisal of the efficacy of such drugs in the relief of pruritus is made particularly untrustworthy because of the subjective nature of the symptom. Baer *et al.* (81) studied the effect of oral Benadryl and Pyribenzamine on [illegible]is), eczematous [illegible]oid dermatosis, [illegible]ni, generalized pruritus, lichen chronicus simplex and dermatitis medicamentosa, and con-

cluded that only 10 per cent of their patients experienced significant relief from their itching Other investigators employing Pyribenzamine (61, 63), Benadryl (61, 63), Neohetramine (58), Thephorin (59), and Trimeton (76) orally in the treatment of atopic dermatitis and contact dermatitis have reported disappointing results. The patch test reaction to poison ivy extract cannot be lessened by administering Pyribenzamine before and at the time of testing and during the development of the reaction (87).

Antihistaminic substances have been incorporated in ointment bases for local application in the treatment of allergic cutaneous disorders and also other skin conditions that are accompanied by pruritus. Perry (88) could not reduce the erythema associated with a histaminic wheal by the local application of a 2 per cent Benadryl ointment, and was also unable to relieve pruritus in patients with itching dermatosis by the local application of such an ointment. Sulzberger *et al.* (89) have observed that 2 and 5 per cent Pyribenzamine ointments have consistent effectiveness only in the local treatment of lichen chronicus simplex and that such ointments are of little value in the management of atopic dermatitis, contact dermatitis, and pruritus vulvae and ani Strauss (90) treated eight cases of bee sting successfully by massaging a 5 per cent Thephorin ointment into the skin at and around the site of the sting. The pain and stinging sensations were reported to have disappeared within one to two minutes after the ointment was applied. The rational for the use of an antihistaminic ointment is based upon the fact that bee venom contains histamine and that histamine is responsible for many of the commoner and immediate manifestations of a bee sting.

Kurtin, Bierman & Yontef (91) first called attention to the fact that areas of skin treated by Pyribenzamine iontophoresis inhibited ultraviolet erythema. Kline & Baer (92) as well as Friedlaender *et al* (93) pointed out that this effect of Pyribenzamine was due to the spectral absorption characteristics of the Pyribenzamine molecule and was not related directly to antihistaminic activity since its ability to prevent ultraviolet erythema was not dependent upon actual contact with the skin. These data have been augmented by Friedlaender *et al* (94) with observations that demonstrate that Neoantergan, Histadyl, Pyrrolazote, Tagathen, Neohetramine, and Antistine, as well as Pyribenzamine, possess absorption bands within the active range of the ultraviolet spectrum (2950 to 3150 Å). Benadryl, Decapryn, Thephorin and Trimeton do not significantly absorb the erythema-producing rays The oral ingestion of the effective antihistaminic compounds prior to exposure to the mercury arc radiations failed to inhibit ultraviolet erythema The effectiveness of many of the antihistaminic drugs in the prevention of ultraviolet erythema stimulated the investigators to ascertain their clinical usefulness as sunburn preventives. Five patients reported excellent protection from 2 per cent ointments of Pyribenzmaine, Neoantergan, Neohetramine and Pyrrolazote.

*Migraine.*—There has been a remarkable paucity of reported observations on the effects of antihistaminics in the treatment of migraine (58, 59, 71,

72, 76). The number of patients treated with various compounds, as reported to date, is so insignificant that no conclusions can be drawn.

*Tuberculosis.*—It has been assumed that the inflammatory reaction that occurs in reinfection with tubercle bacilli or from a spread from the primary focus is partially due to the release of histamine. If this actually is the case, antihistaminic drugs might prevent tissue destruction by protecting sensitized cells from injury. Neohetramine, Pyribenzamine, Benadryl, and Thephorin have been employed in doses of 150 to 400 mg. daily in the treatment of patients with pulmonary tuberculosis over a period of 10 weeks to 7 months (95). In six patients with acute exudative tuberculosis and two patients with acute tuberculous pneumonia, seven displayed x-ray evidence of clearing of the pulmonary lesion, decrease in the amount of sputum and reduction of cough. In six of the patients the first strength P.P.D. Mantoux test reverted from positive to negative. Only four out of fourteen patients with mixed exudative and productive tuberculosis showed an improvement by x-ray, but the first strength P.P.D. test became negative in eleven of the patients. Of eight patients with productive tuberculosis none showed any evidence of improvement but seven out of the eight patients developed a negative Mantoux test to first strength P.P.D. The most significant and hopeful observation of this interesting study was the disclosure that when three patients with acute exudative tuberculosis who were improving were taken off antihistaminic therapy they developed x-ray evidence of retrogression in their pulmonary lesion. Furthermore, reinstitution of antihistaminic substances reproduced subjective and objective improvement.

In regard to the use of antihistaminic drugs in the treatment of infections a note of caution is sounded from the results of recent studies by Halpern in France. The edema in animals accompanying local infections produced by staphylococcus and *Salmonella typhimurium* was inhibited by treatment with Phenergan. The very act of preventing local edema by antihistaminics might very well destroy a natural barrier to the diffusion of the infection, because 80 per cent of the infected animals treated with antihistaminics developed septicemia and visceral abscesses and eventually died, whereas the infected animals that were not treated with antihistaminics recovered (96).

*Motion sickness.*—During the course of time that the clinical effects of Dramamine (β-dimethylamino-ethyl-benzohydryl-ether-8-chloro-theophyllinate) on patients with hay fever and urticaria were being studied in the Allergy Clinic at the Johns Hopkins Hospital it was observed by chance that the drug dramatically relieved motion sickness. Subsequent studies by Gay & Carliner (97, 98) which were conducted on a United States Army Transport carrying soldiers from New York to Bremerhaven, Germany, authenticated without a doubt the efficacy of this substance in the treatment and prevention of sea sickness. Dramamine in doses of 100 mg. every five hours and before retiring prevented sea sickness in all but two of 134 men. Furthermore, the drug effectively relieved the manifestations of sea sickness

within 1 hour after it was administered. Strickland & Hahn (99) have reported that the drug was also efficacious in the prevention of air sickness.

*Miscellaneous conditions.*—Benadryl (100, 101), Pyribenzamine (102), and Thephorin (72) reduce the severity and the duration of subjective and objective symptoms brought on by exposure to cold in individuals hypersensitive to cold. Neoantergan (103) and Benadryl (103) are effective in the management of patients hypersensitive to liver extract. Hunter & Hill (103) have advocated 1 gm. of Neoantergan, in divided doses, twenty-four hours prior to the administration of liver extract. At times it is advisable to give 300 mg. just prior to the injection Severe reactions to liver extract, however, are not modified by Neoantergan. Carryer & Koetsche (104) recommends desensitization with liver extract in addition to the oral administration of 50 mg of Benadryl three to four times a day. As the intervals between liver injections are increased Benadryl is given only on the days of the liver injections Local reactions to insulin may be combatted by mixing insulin with an equal amount of a 1:1000 Benadryl solution. However, such a technique may need to be supplemented by Benadryl given orally if the local reaction is severe or if urticaria is a part of the reaction (105). Horton & Brennan (106) were able to abort attacks of trigeminal neuralgia with 100 mg. of Pyribenzamine given orally. Attacks of trigeminal neuralgia could be precipitated by the injection of 0.1 mg of histamine and immediately relieved by either 100 mg. of Pyribenzamine or 100 mg. of Benadryl administered orally. Thirty mg of Benadryl in 100 cc. of isotonic sodium chloride solution injected intravenously also alleviated the attacks. Bernstein *et al.* (61) reported Benadryl to be effective in the management of two patients with cardiac asthma and in five out of ten patients with functional dysmenorrhea. Trimeton (76) is reported to have provided excellent benefit in one patient and moderate benefit in another patient with radiation sickness. Pyribenzamine (102) does not inhibit the increase of gastric acidity induced by the administration of histamine.

## Side Effects of the Antihistaminic Drugs

There is a definite correlation between the incidence of side reactions and the size of the dose of antihistaminic drugs, but there is no relationship between the type of side reaction that develops and the dosage. Furthermore, there is an individuality of response for each patient as far as different compounds are concerned, and this applies to therapeutic effectiveness as well as to side effects. With few exceptions the quality of the side reactions is similar for all compounds. The quantity of side effects varies according to the drugs and also according to the duration of time that they have been available for study The customary and common side effects, irrespective of compound, are: drowsiness, dizziness, weakness and fatigue, nervousness, tremor, faintness, headache, apprehension, mental confusion, dryness of oral cavity, nausea, anorexia, abdominal pain, vomiting, blurring of vision, paresthesia, tachycardia, palpitation, and urinary frequency (60, 61, 83,

106). The frequency of occurrence of side effects in patients treated with antihistaminic compounds varies from 10 to 50 per cent. Reactions are more prone to accompany the usage of Benadryl, Pyribenzamine, Hydryllin and Neoantergan (60, 61, 63, 65) than Antistine, Histadyl, Neohetramine and Thephorin (58, 59, 60, 66, 73). Trimeton (76, 77) and Decapryn (74) are infrequently followed by side effects, but to date insufficient data have been recorded on these compounds to permit comparison with the other members of the antihistaminic family. Thephorin is unique among the various compounds in that insomnia and nervousness (59, 107, 108, 109) and not drowsiness are the most habitual unfavorable reactions.

The death of a 16 months old child 15 hours after the accidental ingestion of 100 mg of Histadyl has been reported (110). The manifestations of this unfortunate reaction were ushered in by projectile vomiting, followed by drowsiness and periods of clonic convulsions. The body temperature began to rise, accompanied by tachypnea and bradycardia. Prior to exitus the non-protein nitrogen was 240 mg per cent and the carbon dioxide combining power 25 mg. per cent. The patient had been anuric. Necropsy revealed degeneration and fragmentation of the cells in the proximal convoluted tubules of the kidneys with cloudy swelling of the pancreas and liver, splenic congestion, and edema of the lungs and cerebral cortex.

The toxic reactions to Benadryl have been reviewed by Sachs (111), and the reader is referred to this article if reactions are encountered which are not here enumerated. It is necessary, however, to take cognizance of the hard to imagine allergic reactions to these compounds. Bronchial asthma has been exacerbated by Benadryl (112 to 116) and Pyribenzamine (62). Eczematoid dermatitis from Pyribenzamine (117, 118, 119), and contact dermatitis from Pyribenzamine ointment (89, 120) have been encountered.

It is interesting to speculate as to why antihistaminics should at times enhance such clinical manifestations of hypersensitivity as bronchial asthma Is such a reaction the result of the drying effect of these drugs, is it the result of a true hypersensitivity to the chemical compounds, or is it a manifestation of Pellerat's so-called "histaminoid accident," which this investigator claims to be due to the release of histamine from the cell receptors by the antihistaminics? The questions cannot be answered at this time, but certainly the matter is worthy of diligent study.

In selecting an antihistaminic drug for the treatment of an allergic disorder it is as imperative to consider carefully the percentage incidence of its side effects as the percentage incidence of its good results. If it is desirable to avoid drowsiness, Antistine, Histadyl, Thephorin, Neohetramine and possibly Decapryn and Trimeton should be prescribed. When a sedative effect is indicated, Benadryl, Hydryllin, Pyribenzamine and possibly Neoantergan take precedence Optimal results can usually be obtained by using combinations of the various compounds and changing from one to the other as the case demands It is indeed fortunate that a choice can be made from

## TABLE IV

ANTIHISTAMINE SUBSTANCES AND THE FORMS IN WHICH THEY ARE COMPOUNDED

| Common Name | Forms of Preparations made Available for | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Oral Administration | | | | | Parenteral Administration | Local Administration | | |
| | Tablets containing | Capsules containing | Expectorant containing | Elixir containing | Syrup containing | Vials—Sterile | Ointment | Nasal Solution | Ophthalmic |
| Benadryl* Parke-Davis and Company | | a 25 mg<br>b 50 mg | 10 6 mg per 4 cc with 1 6 gr $NH_4Cl$ | 10 mg per 4 cc. | | 10 cc. 1 cc contains 10 mg | 2% (water soluble base) | | |
| Hydryllin (combination of diphenhydramine* and aminophyllin) G D Searle and Company | 25 mg of diphenhydramine 100 mg of aminophyllin | | | 12 5 mg of diphenhydramine and 50 mg of aminophyllin per 4 cc | | | | | |
| Decapryn Wm S Merrell Company | a 12 5 mg<br>b 25 mg<br>(scored) | | | | 6 25 mg per 5 cc. | | | | |
| Pyribenzamine Ciba Pharmaceutical Products Inc. | a 50 mg (scored)<br>b 50 mg (delayed action coating) | | 30 mg per 4 cc with 10 mg of ephedrine and 80 mg of $NH_4Cl$ | 30 mg. per 4 cc. | | | a 2% (petrolatum base)<br>b 2% (water soluble base) | 0.5% | |
| Histadyl† Eli Lilly and Company | 50 mg (delayed action coating) | a 25 mg<br>b 50 mg.<br>c 100 mg<br>d 25 mg (with ephedrine 8 mg) | | | 16 mg per 4 cc | 10 cc. 1 cc contains 20 mg. | 2% (water soluble base) | 0 5% | 0 5% (ointment) |

TABLE IV—continued

| Common Name | Forms of Preparations made Available for | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Oral Administration | | | | | Parenteral Administration | Local Administration | | |
| | [illegible]g | Capsules *containing* | Expectorant containing | Elixir containing | Syrup containing | Vials—Sterile | Ointment | Nasal Solution | Ophthalmic |
| Methapyrilene† *The Maltine Company* | [illegible]rine d to- ng) [illegible]ne d to- mg lon | | | | | | | | |
| *Thenylene*† Abbott Laboratories | [illegible]g. g g. g rine [illegible] g rine ‡ | | | | | | 2% | | |
| Neohetramine Wyeth Inc. | [illegible]g. g g | | | | 25 mg per 4 cc. | | 2% | | |
| Neoantergen *Merck and* Company, Inc. | [illegible]g g | | | | 10 mg. per 4 cc.‡ | 1 cc. contains 10 mg ‡ | 5%‡ | | |
| Antistine Ciba Pharmaceutical Products, Inc | 100 mg | | | | | | | 0 5% | 0 5% (solutions) |
| Thephorin Hoffmann LaRoche, Inc. | 25 mg | | | | 10 mg per 4 cc | | 5% (water soluble base) | | |

TABLE IV—continued

| Common Name | Forms of Preparations made Available for | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Oral Administration | | | | | Parenteral Administration | Local Administration | | |
| | Tablets containing | Capsules containing | Expectorant containing | Elixir containing | Syrup containing | Vials—Sterile | Ointment | Nasal Solution | Ophthalmic |
| Trimeton Schering Corporation | 25 mg (scored) | | | 7 5 mg. per 4 cc. | | | 3% | | |
| Dramamine (8-chlorotheophyllinate salt of diphenhydramine*) G D Searle and Company | 100 mg (scored) | | | | | | | | |
| Tagathen Lederle Laboratories, Inc. | 25 mg | | | | | | | | |
| Pyrrolazote The Upjohn Company | a. 25 mg. b. 50 mg. | | | | | | | | |
| Diatrin Wm. R. Warner Company | 50 mg | | | | | | | | |
| Chlor-Trimeton Schering Corporation | 4 mg. scored | | | | | | | | |
| Perazil Burroughs Wellcomb and Company | 50 mg (scored) | | | | | | | | |

* Identical compounds.
† Identical compounds
‡ Compounds to be made available but not marketed at time article was submitted for publication.

several preparations, and that the preparations are compounded in a variety of forms (TABLE IV).

Before terminating this discussion on the antihistaminic drugs there are a few additional remarks which, I believe, are pertinent. Histadyl, Thenylene and Methapyrilene are simply different names for the same compound. Throughout this review I have used the name Histadyl instead of Thenylene or Methapyrilene, whenever observations have been made on the compound, N-dimethyl-N′-pyridyl-N′-thenylethylenediamine HCl I had no particular reason for the choice of Histadyl other than a desire to eliminate confusion that was bound to exist had I referred to Histadyl in some cases and to Thenylene or Methapyrilene in others. I might have just as well employed Thenylene or Methapyrilene instead of Histadyl. I trust that the various investigators who have reported upon Thenylene or Methapyrilene and the pharmaceutical concerns that market the drug by these names and have, therefore, supplied such drugs to the investigators for study will appreciate my desire to lessen the state of confusion in an era of antihistaminic polypharmacy. Furthermore, Benadryl and Diphenhydramine are, likewise, synonyms Hydryllin is simply a mixture of Diphenhydramine and Aminophyllin. Dramamine is the 8-chlorotheophyllinate salt of Diphenhydramine. Tagathen and Chlorothen differ only in that the former is the citrate salt whereas the latter is the hydrochloride. Chlor-Trimeton and Perazil are undergoing clinical investigation by the Committee on Therapeutics of the American Academy of Allergy at the time this chapter is submitted to the publisher. It is quite likely that both compounds will be commercially available before the data recorded here are published Preliminary reports on Perazil indicate that its action is probably more prolonged than that of other antihistaminic drugs It is to be hoped, therefore, that less frequent administration will provide efficacious results Chlor-Trimeton and the fact that it is a stable compound and not readily destroyed in the body have already been discussed. Simply because the dosage of this drug is smaller than those of other compounds does not imply that side reactions will be less frequent or less severe. As a matter of fact it is reasonable to assume that since the compound is fairly stable it might accumulate in the body should it be given over long periods of time and that toxic side effects, therefore, would be delayed in appearance.

TABLE IV was compiled from data derived directly from the various pharmaceutical concerns interested in antihistaminic substances, and it is hoped that its inclusion will lend to the reader at least a temporary respite from the wanton state of antihistaminic mental untidiness.

### Miscellaneous New Drugs

*Isopropylepinephrine 1-(3-4 dihydroxyphenyl)-2-isopropyl-amino-ethanol (Aludrine, Isuprel).*—Epinephrine possesses excitatory and inhibitory types of actions. The excitatory actions of epinephrine effect constriction of the arterioles and capillaries. The equally important inhibitory actions of epi-

nephrine result in relaxation of the smooth muscle of the gastrointestinal tract and of the bronchial tree

Both the excitatory and inhibitory actions of epinephrine are important in the treatment of patients with bronchial asthma. However, the excitatory action of epinephrine is often followed by prolonged inhibitory action so that congestion of the bronchial mucosa may eventually occur following the administration of epinephrine. This is due to the fact that when the excitatory action wears off the inhibitory action becomes prominent The end result is capillary dilatation instead of constriction.

The excitatory effects of the epinephrine molecule can be diminished and the inhibitory ones enhanced by making substitution in the amino nitrogen portion of its structure. The substitution of an isopropyl group effects such a loss of excitatory action, and the epinephrine-like substance then possesses almost exclusively inhibitory actions. This compound is Isuprel or Aludrine.

The therapeutic effectiveness of Isuprel in the management of patients with bronchial asthma has been carefully studied by Gay & Long (121). Four routes of administration (inhalation, sublingual, oral, and subcutaneous) were evaluated. It was concluded that the inhalation of a nebulized mist of a 1:200 isotonic solution provided the best method of dispensation Patients with mild asthma obtained immediate and complete relief following one course of three to six inhalations. Patients with asthma of moderate severity obtained varying degrees of relief from two courses of four to six inhalations each Even patients with severe asthma who had failed to respond to the usual procedures and medications that they had customarily employed were quickly relieved Improvement was not substantially augmented by employing more than six inhalations in any one course. The duration of relief was inversely proportional to the severity of the symptoms, and benefit in the severe asthmatics persisted for only 15 minutes, while in the patients with milder asthma relief was obtained for from 2 to 12 hours.

A very important favorable effect from the inhalation of Isuprel was the decided increase in expectoration of patients with chronic infective asthma Patients reported their sputum to be thinner, more abundant, and more easily raised. Inhalations of Isuprel also usually provided quicker relief of asthmatic symptoms than inhalations of epinephrine, though the effectiveness was shorter lived.

The administration of 10 mg. pellets of Isuprel for sublingual absorption was found to be the second method of choice because of convenience, rapidity of action, and ability to withdraw the drug in event of unfavorable side effects. The sublinguet was of value in the early treatment of mild asthma, but was not appreciably effective in the management of patients with moderately severe or severe asthma.

The use of Isuprel by oral and subcutaneous administration is both impractical and dangerous because of the high incidence of side effects. The side effects, in order of frequency of occurrence, are as follows: palpitation, nausea, headache, nervousness, tremor, dizziness, precordial ache, weakness,

sweating, anginal pain, epigastric pain, vomiting, tinnitus, flushing of the face, and diarrhea. The incidence of side effects varies according to the route of administration. Four per cent of the patients receiving inhalations, 33 per cent receiving sublingual pellets, 41 per cent receiving subcutaneous injections with a 1:5000 solution, 75 per cent receiving 15 mg orally, 80 per cent receiving 25 to 50 mg. orally and 100 per cent receiving subcutaneous injections with a 1:1000 solution, developed side effects (153).

*Orthoxine; Ortho-methoxy-beta-phenylisopropyl-methylamine hydrochloride*—This compound apparently possesses bronchodilator activity with only slight pressor activity. Graham & Kuizenga (122) reported that Orthoxine was more effective than ephedrine in combating bronchoconstriction produced by pilocarpine, histamine, and acetylcholine in the isolated rabbit lung. In dogs the pressor effect of Orthoxine was found to be ⅛ that of ephedrine and 1/2000 that of epinephrine. Ephedrine was less toxic than Orthoxine when the compounds were compared by intravenous administration to rats and rabbits. However, when the compounds were given orally or subcutaneously their toxicity was of the same order. Because of these pharmacological properties and because, like ephedrine, Orthoxine is not oxidatively deaminated, its clinical evaluation in the treatment of bronchial asthma was indicated.

Curry *et al.* (123) demonstrated that Orthoxine in doses of approximately 200 mg. was comparable to ephedrine in doses of 30 mg. in the protection of the asthmatic patient against asthmatic symptoms produced by the parenteral administration of histamine or Methacholine. Furthermore, the two drugs in the doses cited were comparably effective in relieving patients with mild asthma, but fewer side effects referable to pressor activity were noted from Orthoxine than from ephedrine.

## Hypersensitive Reactions to Drugs and Chemicals

In regard to this important section a few introductory remarks are in order to prepare the reader for the presentation of data that is to follow.

Cutaneous and mucous membrane eruptions of many sorts, asthma, rhinitis, arthralgia, anaphylactic shock, jaundice (obstructive and nonobstructive types), fever, leucocytosis, granulocytopenia, and thrombocytopenia may occur as clinical manifestations of hypersensitivity to chemical substances Any chemical compound, no matter how simple in structure, is capable of acting as a potential sensitizer. An accurate diagnosis of drug allergy is more dependent upon a careful history and the acquired knowledge of its physical manifestations than upon scratch and intradermal skin tests, because such tests with nonprotein chemical substances are rarely, if ever, diagnostic. Eczematous dermatitis which may be provoked by contact with metals, weeds, vines, pollens, flowers, food stuffs, and chemical compounds of varied sorts can be adequately diagnosed by patch testing with the specific causative factor.

The alarming and at times fatal reactions to aspirin, and conversely its

beneficial effects, especially in asthmatic patients, have been observed by every physician possessing a special interest in allergic diseases.

Bronchial asthma is by far the commonest manifestation of aspirin hypersensitivity. Salen & Arner (124) in a study conducted upon 1,464 patients with bronchial asthma reported aspirin hypersensitivity to have occurred in approximately ten per cent of them. The great majority of aspirin-sensitive patients had complications of an infective nature, were over 40 years of age, and were divided equally in regard to sex. Interestingly enough sensitivity to this drug was not observed in children under 12 years of age

The fact that aspirin prevents anaphylactic shock in rabbits sensitized to egg white but does not protect against histamine intoxication suggests that this drug has antianaphylactic properties (125). These experimental data might serve to explain, in part, the beneficence of aspirin in some patients with bronchial asthma. The certitude that aspirin does not always act with such favorable effects and that hypersensitivity to this drug occurs, particularly in patients harboring infection, tempts one to speculate upon the adjuvant role of the infecting agent in provoking hypersensitivity to aspirin as well as to other chemical substances, This thought is not untenable when one considers that lens antibody has been easily produced in rabbits by combining lens substance with staphylococcus toxin (126); that kidney lesions have been produced in rabbits and rats by injecting a mixture of homologous kidney and streptococcus extract (127); and that central nervous system lesions have been produced in monkeys by the injection of monkey brain incorporated in liquid petrolatum and in hydrous wool fat with added tubercle bacilli (128, 129).

The *Trichophyton* fungi play a role in the development of "spontaneous" allergic manifestations to penicillin (130, 131, 132). Peck & Hewitt (133) demonstrated that several strains of *Trichophyton mentagrophytes* elaborated antibacterial substances similar in some respects to penicillin. This fact may or may not be of significance in explaining the "spontaneous" allergic eruptions to penicillin, because there is increasing evidence that previous occurrence of fungous disease accounts for this type of penicillin sensitivity (131). The skin reaction to the intradermal administration of penicillin in these individuals resembles in time of development and appearance the trichophytin reaction, and this delayed reaction to the cutaneous test with penicillin is of practical importance as an aid in the diagnosis of the "spontaneous" type of reaction.

The clinical manifestations of "spontaneous" sensitivity to penicillin characterized by an erythematopapulovesicular eruption which tends to localize first on the hands, the feet, and in the groin and then spread over the body, must not be confused with the serum-sickness type of reaction which is induced by treatment with penicillin.

Urticaria due to penicillin hypersensitivity occurred in 2.5 per cent of 10,000 syphilitic patients undergoing treatment with this antibiotic sub-

stance. Other reactions ascribed to penicillin in this large group of patients were: an exacerbation of secondary syphilitic lesions, papular or erythematopapulovesicular eruptions; local reactions at the site of injection; and rare bullous eruptions (134).

Local reactions at the site of injection are more likely to occur from penicillin incorporated in peanut oil and beeswax than from the aqueous form of penicillin. Four out of 50 patients receiving injections of penicillin in peanut oil and beeswax developed an area of painful swelling in the buttocks at the site of injection, accompanied by a localized erysipeloid cutaneous eruption, fever, and malaise. These reactions reached a peak in 48 hours and receded in 7 to 10 days, leaving a small tender subcutaneous nodule which persisted for another 15 to 45 days. Such a local reaction was not observed in 1,000 patients treated with an aqueous solution of penicillin (135). Two patients who had local instillations of a penicillin solution in only one of their eyes developed edema of the penicillin-treated eye when they subsequently received penicillin parenterally (136). This represents a classical demonstration of the Schwartzman phenomenon.

The eczematous contact type of dermatitis represents a hazard for individuals preparing and administering penicillin (137). Eosinophilia without other manifestations of hypersensitivity typifies the least serious of all reactions to penicillin (138).

Two fatal reactions from penicillin therapy, one preceded by exfoliative dermatitis (139), and the other by anaphylaxis (140) have been reported The cognizance of these mortalities must not inject unintelligent timidity into the hearts of physicians when treatment with this antibacterial agent is indicated. In regard to the patient who died following anaphylactic shock (140), it is important to recognize that the penicillin was accidentally injected intravenously and, furthermore, that penicillin therapy had been advised despite the fact that a previous course of treatment with this drug had been followed by typical manifestations of serum sickness

The eczematous contact type of dermatitis (141, 142), pruritus, rhinitis and conjunctivitis (143), stomatitis (144), and eosinophilia (144) have recently been recognized as clinical manifestations of streptomycin hypersensitivity. Anaphylaxis from the intradermal injection of 0 05 cc. of streptomycin solution occurred in an individual suffering from a contact dermatitis acquired by handling streptomycin (145). This patient had never received streptomycin parenterally and, therefore, had procured her state of hypersensitivity only by contact with the drug.

The eczematous contact type of dermatitis has occurred from monoglyceryl para-aminobenzoate, a filter used in modern sunburn preventives [illegible] (147) from "[illegible]" (148); from tyrothricin

the treatment of conjunctivitis (151) Exfoliative dermatitis from codeine (152); edema of the vulva and glottis from a mixture of demerol and scopola-

mine resorted to for sedation during labor (153); thrombocytopenic purpura from quinidine (154); and bronchial asthma, angioneurotic edema, and pruritus of the face and anus from accidental contact with salvarsan which was in turn absorbed through a skin abrasion (155) have been reported during the past year.

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# NEOPLASTIC DISEASES

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## Introduction

The biological sciences during the recent years have contributed a number of significant facts regarding or directly applicable to neoplastic diseases. Not yet, however, has the point been attained where the established information regarding cancer permits of synthesis into a clear and readily distinguishable pattern

There is an ever-increasing extension of research activities on cancer, made possible by broad, intelligent public interest and professional support. Funds available for investigations on cancer in the United States alone have mounted from approximately one million dollars in 1940 to 18 millions in 1948 (1). Experimental data from many scientific disciplines, some demanding verification and others which may be immaterial or actually misleading, crowd the massive literature (2) There are now four journals in the English language that are devoted exclusively to cancer. Valuable monographs (3 to 6), reviews (7 to 10), and symposia (11 to 14) have attempted to present and to evaluate the available information. The Fourth International Cancer Congress, held in 1947, summarized many research activities since the war (15).

Optimism concerning the eventual solution of the cancer problem is justifiable because of the broad advances being made in the physical and biological sciences. Tools such as the cyclotron, mass spectrograph, ultracentrifuge and electron microscope, and the developing techniques of microchemistry and cytochemistry, isotope tracers and tissue culture, make increasingly feasible the exploration of the cell, its component parts and its dynamic states. And the secret of cancer lies within the cell.

There are three basic questions in cancer research (*a*) carcinogenesis, or the process by which normal cells or tissues become transformed into cancer; (*b*) the nature of the cancer cell, or the physiological and biochemical differences between normal cells and their neoplastic counterparts, and (*c*) the tumor-host relationships, or the changes that occur in an organism in which a neoplasm is developing or has become established. The practical questions regarding the prevention, diagnosis and treatment of cancer in man are probably dependent upon, and will follow in direct relation to, the extent that the fundamental problems are clarified.

## Carcinogenesis

*The host.*—Cancer, as all physiological or pathological conditions, is a result of the reaction of an organism or its tissues to certain stimuli. All

animals appear to be susceptible to neoplasia, despite occasional reports of purported cancer-free species.

There is a wide difference between species in their susceptibility to cancer, although such differences become reduced as the species is more thoroughly studied, particularly in older age groups. Monkeys apparently develop but few malignant tumors (16). The mouse develops almost all types of neoplasms that are observed in man, which makes this animal particularly valuable to cancer research, since geneticists have established numerous homozygous strains which allow exact genetic studies (17, 18). Marked differences in susceptibility to specific types of neoplasia are evident in various inbred strains of mice and rats.

Abnormalities of cellular growth indistinguishable from cancer as seen in mammals and birds also occur in cold-blooded vertebrates (19) and insects (19a). Plants also develop cellular overgrowths resembling neoplasms (20).

Any organ or tissue may be the site of neoplastic growth. Even the lens of the eye, in which spontaneous malignant growth has not been described, has been shown to be susceptible to neoplastic transformation (21). Recent evidence (22) suggests that embryonic tissues may be more susceptible to carcinogenic transformation than adult tissues (23). When embryonic tissues are exposed to methylcholanthrene and then transplanted into animals of the same strain, neoplasms are observed within 20 to 40 days, a considerably shorter period than is seen for tumors induced with this carcinogen in adult animals.

Earle (24) and Gey (25) have demonstrated that sarcomas can develop from fibroblasts grown in tissue culture. This important contribution of carcinogenesis *in vitro* proves that the neoplastic change can occur without the intermediation of the whole organism. Established information indicates that all cells or groups of cells which can divide also possess, in varying degrees, the inherent properties which, under certain conditions, lead to neoplastic transformation. Imaginative theories regarding the origin of all neoplasms from hidden embryonic nests or invisible totipotent cells have no substantiated support.

Cancer, being a cellular reaction, is obviously influenced by all factors that influence the cell, either directly or through more complex pathways involving the whole organism. Thus the incidence, type and speed of the reaction is the result of a chain of processes directed by both genetic and environmental factors. There is no evidence that a single gene determines the presence or absence of cancer, but certain genes and combinations of genes exert definite influence on the susceptibility of the organism to specific types or groups of neoplasms. The soundest demonstrations of the role of genetic factors in the development of cancer are afforded by the classical experiments on mammary (11) and on pulmonary (18) tumors in mice. Different genetic and physiologic mechanisms, therefore, may be involved not only in different types of neoplasia but even in similar neoplasms that

arise following different types of stimuli. This appears to be the case in spontaneous leukemia, in leukemia induced by polycyclic hydrocarbons, and leukemia induced by radiation in mice (18, 26).

Noncontroversial information on genetic factors involved in neoplasia in man is extremely limited, particularly because of the heterogeneity of the species. A recent symposium (27) on the subject indicated that a considerable number of neoplasms and precancerous conditions, particularly xeroderma pigmentosum, neuroblastoma of the retina, and multiple polyposis of the colon, appear to have strong hereditary factors. In addition, cancer of the breast, uterus, and rectum and leukemia, may show hereditary tendencies. It was stated that many of these tumors may be inherited as characteristics showing incomplete dominance, although the possibility of multiple factor inheritance cannot be excluded. The tendency to tumor localization also has suggestive hereditary basis.

The development of cancer in a species has been shown to be influenced by a wide variety of changes in the internal and external environments of the host. The degree of effect on the development of neoplasms may be correlated roughly with the degree or extent of such changes. The aspects of internal environment that have been studied most thoroughly are the hormonal status and nutrition.

Hormonal imbalance in mice leads to the appearance of at least five types of tumors in tissues especially dependent upon hormonal secretions in their physiology (28). Excessive estrogenic stimulation, endogenously or exogenously supplied, leads in appropriate strains of animals to the development of mammary, testicular, or cervical tumors. Oophorectomy, causing gonadal deficiency and pituitary hyperfunction, reduces the number of mammary tumors, but in one strain of mice (29) induces adrenocortical carcinomas which in turn can be prevented by an exogenous supply of estrogen Ovarian tumors in rats or mice can be produced by the ingenious technique (30) of transplanting ovaries into the spleen of castrate animals, thus producing gonadal deficiency through deactivation of estrogens by the liver and compensatory production of gonadotropic pituitary hormones.

In general, the incidence of tumors in mice can be lowered by placing the animals on restricted diets. Reduction of the *ad libitum* caloric consumption by one-third practically eliminates the appearance of mammary carcinoma (31) Reduction in specific dietary constituents also influences the incidence and time of appearance of certain neoplasms Mice on low cystine diet develop less methylcholanthrene-induced leukemia than animals on full diet (32). The effectiveness of azo dyes in producing hepatomas in rats appears to parallel its effectiveness in lowering hepatic riboflavin, and certain diets are protective against the carcinogenic effect in relation to their riboflavin content (33).

The incidence and time of appearance of neoplasms can be affected by other environmental factors. It has been reported (34) that mice kept at higher environmental temperatures develop more and earlier mammary

tumors than those kept at lower temperatures. Mammary tumors appear at an earlier age in mice kept in isolation than in animals sharing the same limited quarters (35). It is evident that the number of such influences is almost limitless, and that they may be interrelated; one factor may produce secondary effects, such as the influence of diet on hormonal metabolism, or the influence of isolation on food intake and temperature. Moreover, the hormonal and nutritional physiology are also affected by the genetic background of the organism, as shown by studies on the "inherited hormonal influence" in the etiology of mammary tumors in mice (36).

*The stimulus*—Cancer research has been advanced by discoveries of numerous agents which produce a wide variety of malignant neoplasms. The induction of tumors by these carcinogens implies no more than that after the exposure of an organism to an agent, the incidence of certain tumors is significantly increased. As such, the distinction between "spontaneous" and "induced" tumors is that the former are of unknown etiology whereas the latter arise following known application of some agent or procedure. It is not possible to state that a particular agent is the direct cause of the neoplasm; the actual carcinogenic stimulus might be some metabolic derivative or exert its effects through other devious physiological processes.

There are three known classes of carcinogenic agents: (*a*) chemical, (*b*) physical, and (*c*) viruses. More than 400 chemicals of greatly diverse molecular structure are known to be carcinogenic under certain conditions and in certain species.

During the decade following the discovery by Kennaway and his group (14) of *1, 2, 5, 6-dibenzanthracene and 3, 4-benzpyrene*, emphasis was placed on the study of these and related polycyclic hydrocarbons which induce a wide variety of neoplasms in rodents, particularly at the site of injection (37). Soon thereafter, many investigations were carried out with the azo dyes, such as *p*-dimethylaminoazobenzene and *o*-aminoazotoluene, which produce tumors of the liver when fed to, or injected into, rats or mice (10, 14, 38).

Carcinogenic chemicals which have been of considerable recent interest in research include: urethane (ethyl carbamate), which causes pulmonary tumors in mice and rats (39, 40); carbon tetrachloride, which leads to the development of hepatomas in mice (41); 2-acetyl-aminofluorene and related compounds, which on ingestion induce tumors of the liver and breast in mice and rats (42, 43); and thiouracil, which on prolonged administration produces nodular tumors in the thyroid (44).

The estrogenic compounds, such as estrone or diethylstilbestrol, produce mammary, *cervical, testicular, and pituitary tumors in mice* (11, 14), and mammary, pituitary, and bladder tumors in rats (45). Reports (46, 46a) on the appearance of mammary cancer in men receiving prolonged administrations of diethylstilbestrol indicate that these compounds are also carcinogenic in human beings.

The estrogens still represent the only chemically defined compounds of

normal animal metabolism which have been shown conclusively to be carcinogenic. Sarcomas in mice at the site of injection of nonsaponifiable lipid fractions of human livers and other tissues (47), have been postulated to be due to some endogenously produced carcinogens perhaps related to the polycyclic hydrocarbons. It has been reported (48) that occasional sarcomas in mice can be produced by commercial cholesterol, especially when dissolved in lipids. Sodium desoxycholate also has been stated to induce occasional subcutaneous sarcomas and to increase the incidence of pulmonary tumors in mice (49).

Ionizing radiations, whether delivered from external sources or administered in the form of fission products, have carcinogenic properties. Single exposures of mice to 90 to 700 r lead to an increase and earlier appearance of leukemia and to the appearance of ovarian tumors. Chronic exposure to up to 8 8 r per day results in increased incidence of mammary carcinoma and sarcoma, ovarian tumors and pulmonary tumors (50, 51). Local fibrosarcomas and osteosarcomas are obtained in mice, rats and rabbits with parenteral administration of radioactive fission products and of plutonium (52). Another form of physical energy which is established as carcinogenic is ultraviolet radiation in the 2,900 to 3,300 Å range, producing cutaneous and subcutaneous tumors in mice and rats, and probably some skin carcinomas in man (53).

Of great interest as carcinogenic agents is the group of self-reproducing macromolecular protein entities, the viruses. They are involved in the causation of sarcomas and lymphomatosis of fowl, and in Shope papilloma of rabbits. The agent in the milk necessary for the development of most carcinomas of the breast in mice is an agent with many virus-like properties (11, 54). Ultracentrifugal separation of mouse mammary carcinoma indicates that the milk agent is associated with macromolecular particles with a molecular weight of three to five million (55, 56). Similar particles have been extracted in the past from normal as well as neoplastic tissues (55), and one ultracentrifuge study (57) suggests that the active agent of the chicken sarcoma may be much smaller in size than generally assumed. The transplantability of mammary tumors in mice does not depend upon the presence of the milk agent (54), and mammary tumors may develop in mice presumably devoid of the agent (58). The Shope virus also may disappear, or become no longer detectable, in later transplants of carcinoma initially induced by the agent (59).

It is not clear where neoplasms following infestation with larger parasites should be classified. Examples of such infestation leading to neoplasms are the sarcomas of the liver of rats infested by *Cysticercus crassicolis* Sarcomas of the peritoneum can be produced by ground-up larvae, and the active agent is associated with the calcium carbonate corpuscles of the parasite (60) In man, invasion of the bladder by *Bilharzia haematobium* leads to the development of cancer (61), no studies on the active agents involved are available

Less than one per cent of neoplasms of man can be ascribed to industrial or other environmental exposure to carcinogenic agents. A comprehensive survey by Heuper (62) enumerates no less than 19 chemicals or crude products of etiologic significance in human cancer. More conservative evaluations question the activity of many of these agents, particularly those in crude form. Chemicals such as crude anthracene, arsenic, creosote, oil shale, pitch, soot, spindle oil, and tar, cause cancer of the skin. Radioactive substances are incriminated as carcinogens of the blood forming tissues and bone as well as skin. Of interest are β-naphthylamine, which causes carcinoma of the bladder, and chromates, which recently have been incriminated in pulmonary cancer (63).

*Mode of action.*—Except within a narrow range of specific types of compounds and specific types of neoplasia, the wide diversity of chemicals with the property of eliciting cancer appears to preclude any precise correlation between molecular configuration and carcinogenicity. The trend of research has now been extended to the more cogent considerations of their metabolism and mode of action.

Studies continue on the distribution, metabolic conversion, and elimination of polycyclic hydrocarbons, azo dyes and acetylaminofluorene (10,14), including the appearance of products of 3, 4-benzpyrene following intravenous administration in man (64). The techniques of detection by chemical or spectrographic methods have been extended by the use of radioactive tracers incorporated into the structure of 1, 2, 5, 6-dibenzanthracene (65) The material is metabolized by the mouse into at least four substances and is rapidly eliminated, largely through the feces. Metabolites of the azo dyes and aminofluorenes are excreted chiefly in the urine. In general, the metabolites so far tested show a loss or great reduction in carcinogenic activity. The understanding of the detoxification of carcinogens, often administered in grossly excessive doses, contributes essential information, but casts little light upon the actual process of neoplastic transformation.

Of greater significance have been the important studies by Miller & Miller (66) which show that *p*-dimethylaminoazobenzene on ingestion by the rat binds tightly with the proteins of the liver cells. Dissociation of the combination is achieved only by degradation of the protein. Bound dye is not present in other rat tissues where tumors are not induced, or in blood proteins. Lower levels of binding occur in mice, which are more resistant than rats to the hepatomagenic action of the chemical, and no binding occurs in several species in which liver tumors are not induced The proteins of rat hepatomas no longer have the property of binding with the azo dye, indicating that an essential alteration has occurred in the cellular protein.

It has been established that a wide variety of chemical carcinogens also have the property of being able to induce germinal mutations. This was first claimed by Strong (67) with methylcholanthrene in mice and subsequently reported with 1, 2, 5, 6-dibenzanthracene (68) Some twenty compounds were assayed by Demerec (69) for mutagenic properties, using *Drosophila*

exposed to aerosol mists containing the chemicals. There was surprisingly good correlation between carcinogenicity in mice and mutagenicity in *Drosophila*.

Detailed observations on the histogenesis of pulmonary tumors (70) and hepatomas in mice (41) dissociate an inflammatory reaction as a necessary precursor of neoplasia. The conclusion has been questioned by claims (71) that pulmonary tumors in mice following carcinogens arise in foci of chronic collapse inflammation. Associated induced chronic inflammation, however, does not increase the number of pulmonary tumors evoked with methylcholanthrene (72). When croton oil is painted on the skin of mice after the application of a carcinogenic hydrocarbon, the number of tumors developing locally is increased. This effect is not obtained when the inflammation is produced prior to the carcinogen application, indicating that inflammation exteriorizes more rapidly specific changes elicited by the carcinogen (73).

One of the few long-term systematic examinations of changes that occur in a tissue exposed to a carcinogenic agent has concerned itself with epidermal carcinogenesis in mice painted with methylcholanthrene (74). Morphological and biochemical alterations were studied as the skin went through precancerous hyperplasia to fully developed epithelioma. In the former phase, there is marked increase in the cell and nuclear volumes, mitotic frequency, cytochrome oxidase, and arginase, and decrease in the total-lipid/protein-nitrogen ratio, calcium/nitrogen-phosphorus ratio, iron/nitrogen-phosphorus ratio and biotin. In cancer, many of these changes persist, but others are altered or reversed. It is difficult to estimate the significance of these changes, particularly since no comparisons were made with effects of noncarcinogenic hydrocarbons. The investigators postulate that the decrease in calcium (75) and the possible role of hyaluronidase (76) may be of importance in explaining decreased cohesiveness and the invasive properties of cancer.

## Nature of the Cancer Cell

*Biological*.—The biological properties of the cancer cell, or more correctly groups of cells recognized as cancer, were discerned before the twentieth century on the basis of gross and microscopic examinations of clinical material. The basic characteristics are autonomy and anaplasia (6, 77) Both are relative terms distinguishing cancer quantitatively from normal processes of growth and differentiation.

Autonomy is the disregard by cancer for normal limitations of growth The penetration of normal tissue boundaries by cancer and the occurrence of metastasis still represent the best evidence of malignancy. Neoplasms show a wide variation in the degree of autonomy Some transplantable tumors in animals will grow in practically every site of inoculation and in almost every strain of the species. Others, such as most interstitial cell tumors of the testes in mice, which grow only in estrogenized animals, survive and proliferate under specialized conditions. Similar relative autonomy is encoun-

tered in man, such as the partial dependence of some mammary cancers upon the hormonal substrate of the host. Usually the autonomy of tumors is limited to hosts of closely related genetic constitution, but some will grow under specific conditions in unrelated hosts, such as in the anterior chamber of the eye (78).

Anaplasia in tumors refers to loss of organization and of useful function There is a wide spectrum, from tumors closely resembling normal tissue and continuing to perform some functions of the normal counterparts, to neoplasms so disorganized that no guess can be made regarding the tissue of origin. The chief activity of most neoplasms appears to be self-propagation They have characteristics which no longer fit them into the body physiology, which depends upon intricate and well-balanced adjustments, but obey their own laws of unbridled initiative at the expense of the well-being of the host. This departure from normal growth, including embryonic growth, may represent either the acquisition of new properties or the loss of control mechanisms present in normal cells. It has been pointed out repeatedly (77) that the rate of growth alone is not a criterion of neoplasia, since many normal growth processes exceed the growth rate of many tumors.

Fully established neoplasms maintain their appearance and other characteristics as constantly as any other biological material, recapitulating their cellular properties through fission. They reproduce "true to type" in metastatic sites, upon transplantation into compatible hosts, in heterologous eyes (78), in developing eggs (79), or in tissue culture. Alterations in structure and behavior occur, of course, usually as "dedifferentiation" toward decreased organization. Particularly with pulmonary and mammary tumors of the mouse, transition of carcinoma to a tissue which morphologically has to be designated as sarcoma is seen rather often It is probable that mutations occur in neoplasms (17). Occasional regression and disappearance of malignant neoplasms in original or homozygous hosts is usually attributable to interruption of their nutrition, such as by vascular occlusion, rather than to loss of neoplastic properties or other alterations in the neoplastic cells themselves. In heterozygous hosts, lack of growth or survival of tumors is attributable to immune reactions to foreign tissues or their proteins.

All evidence points to the assumption that the initiating external stimuli leading to cancer, such as carcinogenic compounds, do not have to be present for the continued reproduction of cancer once the neoplastic transformation has occurred. The initiating stimulus creates some hereditarily transmissible change in the cells which then continues through successive generations of division. This characteristic sharply divides neoplasms from other forms of pathological changes of tissues

Numerous observers have attempted to find and to describe morphological differences between normal and neoplastic cells that could be stated to be specific for neoplasia. Since any tissue is susceptible to neoplastic transformation, and since tumors often closely resemble such tissues of origin, it is not surprising that no such universal characteristic has been found. Sig-

nificant changes are detectable, however, when specific neoplasms are compared with their tissue of origin. There is an alteration in the nucleus-cytoplasm relationship, and histochemical studies have shown increased amounts of ribosenucleic acid in neoplastic cells, suggesting that the heterochromatic region of the chromatin is significantly altered (80, 81). A rich literature (82, 83) exists on the chromosomal aberrations seen in neoplasms, including irregularity, suppression of the spindle, and alterations in size and number. Such changes are at least partly attributable to decreased food supply, toxic products, and other environmental influences on tumor cells rather than being specific characteristics of neoplasms (83).

Electron microscope studies on the macromolecular components of the cytoplasm and other regions of the cell may yield significant observations, but up to the present the data (84, 85) are too sparse to be evaluated.

*Biochemical*—Extensive biochemical studies on neoplastic tissues for the most part correlate in biochemical terms the general biological properties of tumors The loss of organization and function, i.e , anaplasia, are demonstrated by reduction or loss of specific enzymatic systems of specialized tissues of origin There is usually a diminution in respiratory enzymes such as cytochrome and cytochrome oxidase.

Neoplasms as a whole tend to converge toward a common biochemical class, showing less diversity than normal tissues (3). This general conclusion is based upon studies with transplantable tumors which are highly selected, fairly homogeneous as to cell type and usually rapidly growing. The observations suggest that tumors may form a separate type of tissue regardless of etiology or histogenesis Scattered data on enzyme systems (86) or vitamin content (87) of spontaneous neoplasms in man show as great a diversity of values in neoplasms as in normal tissues, but such data are seldom corrected for the stromal elements of the tumor. Glutamine and asparagine are split faster by hepatoma than by liver extracts (88), and there is much greater incorporation of certain amino acids into hepatoma slices than into liver slices (89). The increased rate of protein synthesis by hepatoma may be related to decrease in activity of certain proteolytic mechanisms There is accumulating evidence that decreased rate of catabolism may be an important feature in the progressive growth of tumors.

Glycolysis under aerobic and anaerobic conditions, established by Warburg (2, 9), remains as one of the most constant and significant differences

shown that, as in normal tissues, the phosphorylative glycolysis of tumors operates through the Embden-Myerhof scheme

Searches for specific abnormal constituents in neoplastic tissue that would be absent in normal tissues have been actively but unsuccessfully pursued. Newer methods of fractionation and analysis of tissue components, however, have revitalized such investigations. Polarographic analysis indicated the

presence of an abnormal lipid in epidermal carcinoma of mice (90a), and an antigenic lipid was extracted from a human mammary carcinoma (90b). An abnormal cryoglobulin, electrophoretically homogenous, was found in the lymph nodes and serum of a case of lymphosarcoma (90c).

*Cancer theories*—Of the many theories regarding cancer that have been presented during the past century, two appear to have the greatest amount of objective support and deserve critical consideration. These are the somatic mutation theory and the virus theory. Both seek to explain the transmissible, inherited characteristics that cells acquire in their conversion to neoplasia: one, through mutational changes in the genes of the cell, the other, through the invasion of, or activation in, the cell of semi-independent entities in the cytoplasm (9, 77).

The theory of somatic mutation implies that cancer is the result of a physical or chemical change in the genes of the cell. Many of the known carcinogens also have the property of inducing germinal mutations, and it is quite possible that similar effects can be produced in somatic cells The difficulty of proving this concept is that cancer cells, as all somatic cells, reproduce asexually and no tests for true genetic mutation can therefore be made.

The virus theory of cancer implies that neoplasia is an invasion or activation of self-reproducing protein particles within cells, resulting in a cell-virus symbiosis which persists through subsequent divisions of the cell, stimulated by similar divisions of the virus The etiologic role of virus entities in certain neoplasms of the fowl, mammary tumors of mice, and some skin carcinomas of rabbits is noncontroversial. Whether the continued presence of such entities is necessary for the maintenance of the neoplastic process, and whether such entities are involved in other forms of neoplasia, however, remain to be demonstrated.

There is good reason to believe that these apparently widely divergent theories can be reconciled, largely on the basis of the work of geneticists during the past decade. Classical chromosomal genetics is insufficient to account for the widely divergent differentiation of somatic cells whose genes are identical. Significant work on plastids in plants, on the killer factor of *Paramecia* by Sonneborn, on carbon-dioxide susceptibility of *Drosophila* by L'Heritier, and on adaptive enzymes of bacteria by Spiegelman and others, have established that "transmission of cytoplasmic characters actually exists" [Caspari (91)]. Macromolecular constituents of the cytoplasm, therefore, may have or may acquire the properties of transmissibility and mutability (92). Inheritance through cytoplasmic entities is of course in no way contradictory to the role of the nucleus and the genes, since all must be in balance and adjustment in order for the cell and its descendants to survive (93).

A number of thoughtful papers (94, 95) have appeared suggesting that variant cytoplasmic entities may be responsible for neoplasia. Available knowledge is insufficient to indicate whether such entities gain access to the

cell from without, or are mutant forms of normal cytoplasmic particles, or are formed under certain stimuli from the proteins of the cytoplasm.

The importance of these hypotheses lies in the fact that the biological sciences appear to have reached a stage where they may be susceptible to factual experimentation The great strides being made in the chemical and physical isolation and definition of protein components of the cell will lead to a careful comparison of such constituents derived from normal and neoplastic tissue, particularly if such cells can be grown on tissue culture in artificial media. Reports are appearing which suggest differences between nucleoproteins of tumors and their normal counterparts (96) The most sensitive methods available at present for such differentiations are the immunochemical techniques, which often can distinguish specific molecular arrangements and patterns of proteins and other compounds. Interesting steps in this direction have been taken in the work of Kidd (77) who has demonstrated distinctive constituents in two transplantable tumors, and in the work of Macula (97), who indicates that nucleoproteins derived from mouse tumors are immunologically distinct from normal mouse organs. Irrefutable proof of the concept, however, would be based on the removal of definite entities from tumors and the conversion of normal cells to neoplastic cells by exposure or injection of the material So far, this has been possible only with the known tumor viruses, either in animals or in tissue culture Relevant reflections are made by Medawar (98) on the transmission of cytoplasmic pigment granules of the guinea pig epidermis. It is also stimulating to imagine that the transformation of pneumococcal types by exposure of the organisms to nucleic acids (99) may have connection to the suggestive preliminary note on the possible transformation of renal tumors in frogs to normal tissues in the regenerating limbs of salamanders (100).

## Tumor-Host Relationships

The development and the growth of a neoplasm in an animal produces many profound effects, not only at the site of the tumor but in tissues and systems distant to the tumor itself. Cachexia, anemia, and the hepatic dysfunction in patients with gastrointestinal cancer are examples frequently encountered clinically. In animals, the catalase activity is lowered in the liver and kidneys, the red blood cells and hemoglobin decrease, the blood proteoses increase, tissue and blood aldolase increases, the serum and tissue esterase decreases, and fatty material is lost from the suprarenal cortex. These effects are seen with a variety of neoplasms, and may be reversed upon the removal or regression of the tumor. Although most of them become detectable when the tumor weight is an appreciable fraction of the body weight of the host, some are not correlated simply to the size of the neoplasm or the degree of general debility of the host. Although none is established as unique for tumor growth, the effects are not due merely to the presence of growing tissue (3, 9, 101).

The decrease in the lipids of the suprarenal cortex and altered patterns of steroids that appear in the urine of patients with advanced cancer suggest abnormalities in the metabolism of suprarenal cortical hormones. A systematic, detailed extraction and identification of steroids from urine of normal individuals and patients with cancer by Dobriner *et al.* (102) have led to the separation of over 40 compounds. There is accumulating evidence that not only do quantitative patterns of these steroids change in the presence of cancer, but that at least one steroid, $\Delta^9$-etiocholenolone, is found predominantly in the urine of cancer patients and only rarely in the specimens of normal subjects (103).

The significance of isolated studies on specific constituents or enzyme systems of urine or blood of patients with cancer is not clear. Electrophoretic observations on plasma proteins suggest an elevation of an acid protein component (104); a serum polysaccharide appears to be elevated in the presence of tuberculosis and of cancer (105); blood from carcinoma patients showed a higher inhibition of hyaluronidase activity than normal blood (106); mucoproteins are isolated in larger quantities from cancerous blood than from normal blood (107). It is of interest that in the presence of cancer, as well as in other disease states, there is disturbance in the proteins of the blood and diminution in its reducing power, probably due to lowering of the sulfhydryl content (108).

In contrast with the systemic effects of neoplasms in general, certain definite effects are produced by specific neoplasms, as a result of hyperfunction maintained from their tissue of origin Manifestations of hormone-producing abnormalities are seen with tumors derived from hormonal tissues. hyperinsulinism with tumors of the islands of Langerhans, hyperepinephrinism with pheochromocytoma, increased 17-ketosteroid excretion with suprarenal tumors, excessive gonadotropins with testicular carcinoma, and masculinizing effects with arrhenoblastoma of the ovary. Increases in the serum acid phosphatase with disseminated prostatic carcinoma, serum alkaline phosphatase in osteogenic tumors, and appearance of melanin in patients with metastatic melanoma also have been established as diagnostic procedures of considerable value.

## Diagnosis and Treatment of Cancer

*Diagnosis*—In the field of clinical diagnosis of cancer, the biopsy remains as the only acceptable proof of the presence of a neoplasm. Reports implying high accuracy in the diagnosis of cancer by various biochemical or biological procedures appear constantly, but all such tests remain unestablished and there is no sound evidence that any are specific for cancer.

The biopsy has been extended and augmented by the recent techniques for the study of exfoliative cytology. Often the earliest changes in carcinoma are reflected in the nuclear structure of the superficial cells, which become exfoliated and discharged in the cavities of the body. Impressive results have been obtained in the early diagnosis of carcinoma of the cervix by the

methods developed by Papanicolaou & Traut (109); in trained hands (110) the accuracy of the procedure exceeds 95 per cent. The method is applicable not only in diagnosis but for the wider public health use as a screening procedure. The procedure has now been extended to other organs and tissues, with increasing accuracy as experience accumulates. Particularly noteworthy are the percentages of correct diagnoses that are being achieved and being constantly improved in bronchogenic carcinoma, by smears of sputum or bronchial secretions (111), in carcinoma of the bladder, by examination of the urinary sediment (112), and in carcinoma of the stomach by cytological study of gastric washings (113).

The application of radioactive tracers to the diagnosis of tumors is a fertile field for investigation. The increased uptake of radioactive phosphorus in superficial tumors of the breast is of occasional clinical help (114). Both radioactive phosphorus and radioactive iodofluorescein (115) have been reported to be of some use in the localization of brain tumors, before and during operation

*Treatment.*—Several comprehensive reviews (13, 14, 116, 117) have indicated the difficulties that are faced by investigators in search of effective therapeutic agents against cancer A number of chemicals have been introduced into clinical investigation which show definite objective effects on certain types of neoplastic growth in man; all such effects thus far are of a temporary alleviative nature only.

The cure of neoplasms at present remains firmly with surgery and with radiation therapy. The general trend in surgery for cancer is toward more radical excision, made possible by the great developments in anesthesiology, blood and electrolyte replacements and antibiotics Progress in radiation therapy is referable to advances in the pathways and dosimetry of administration. The medical uses of radioactive substances (118) are being avidly explored, although only radioactive phosphorus in erythremia and leukemia, and radioactive iodine in thyroid disease and a small percentage of thyroid neoplasms, have reached the stage of clinical application The full development of this important field is still in the future.

Urethane (ethyl carbamate), given in oral doses of 3 to 6 gm per day, produces clinical improvement in chronic leukemias (119). In 57 cases of chronic myelocytic leukemia gathered from five series (117), a satisfactory response was achieved in 49 patients; in chronic lymphatic leukemia, 21 of 43 patients responded satisfactorily. Urethane is a bone marrow depressant, and its effects in leukemia in many ways resemble those achieved previously with Fowler's solution (potassium arsenite) and with benzol As with all other forms of therapy for leukemia, including radiation therapy, the alleviative effects are not reflected by increased longevity of the patients (120).

The amine mustards [methyl bis (beta-chloroethyl) amine hydrochloride and related compounds] have had wide clinical trial They are administered in intravenous doses of 0.1 to 0 6 mg. per kg. body weight and have marked

depressive effects on the bone marrow. The agents are useful adjuncts in the treatment of Hodgkin's disease, leukemia, lymphosarcoma, and mycosis fungoides A summary (121) of seven series of more than 200 patients with Hodgkin's disease treated with amine mustards indicates that a remission of the disease can be expected in over 90 per cent of patients who are in good physical condition and who had not been treated with roentgen rays; only 50 per cent of the patients who have had this disease for three years or more and who no longer respond to roentgen therapy will show some beneficial effects from amine mustard therapy. The average remission period achieved with amine mustards in Hodgkin's disease is three months, and there is no evidence that the life span is prolonged. Dramatic remissions are achieved in many cases of mycosis fungoides; the results in other lymphomas are somewhat less satisfactory. Objective temporary improvement was obtained with amine mustards in 19 of 41 cases of bronchogenic carcinoma (122).

The anti-folic acid compounds (such as 4-amino-pteroyl-glutamic acid) have shown some temporary effects on the clinical condition and course of patients with acute leukemia, particularly in children. Remissions of up to a few months are claimed in approximately 50 per cent of children (123), but other series indicate the more usual experience of ephemeral effect in approximately 20 per cent of the cases.

Stilbamidine (4, 4'-diamidinostilbene) and related compounds (124) produce subjective relief of pain in multiple myeloma, but objective signs of of improvement are extremely rare In a summary of 186 cases (116), 25 per cent had complete relief of pain and another 38 per cent had partial relief of pain following parenteral injections of the drug Stilbamidine, and to a lesser extent pentamidine, causes fifth nerve neuropathy in approximately 15 per cent of the patients, and also has acute toxic effects on the myocardium (124a)

*S. marcescens* (*B prodigiosus*)polysaccharide, which produces hemorrhagic effects in mouse tumors, has been tried clinically (13) and reports on some 20 cases are available in the literature. The agent produces high fever, leukocytosis, and a severe drop in blood pressure. Occasional decrease in the size of sarcomatous or lymphomatous tumors, and clinical improvement of the patients have been observed, but the treatment is hazardous and seemingly unpredictable.

The most striking results in disseminated carcinoma are obtained with castration or estrogenation in patients with carcinoma of the prostate. The classical work of Huggins (125) has now been extended to observations of five-year results. Of 20 cases of disseminated prostatic cancer treated by orchiectomy, 18 showed a favorable response, five years later, four had no clinical signs of malignancy. Thus, a 20 per cent arrest rate was achieved in a group of otherwise hopeless patients Similar results are produced by estrogen therapy. Of 200 cases of prostatic carcinoma treated with diethylstilbestrol (126), 75 per cent showed regression of the primary growth and 45 per cent had regression of metastases The average survival of these cases

was also definitely increased to about four years, as compared with the previous survival of approximately eight months.

The recent interest in the occasional temporary arrests of widespread mammary carcinoma by interference with the hormonal status of the host is a recrudescence of an old topic (11). The availability of a large number of chemicals with estrogenic and androgenic properties has led to their clinical application in disseminated mammary carcinoma (127). Testosterone propionate, injected intramuscularly three times a week for 10 weeks in 100 mg. doses, and followed by oral methyl testosterone in doses of 60 mg. per day is recommended in premenopausal women. It is particularly indicated in the presence of osseous metastases but also affects soft tissue metastases Subjective improvement was achieved in about 60 per cent, and objective evidence of regression and recalcification was noted in about 20 per cent of 285 patients (127). Estrogens, usually in the form of diethylstilbestrol given orally in doses of 5 to 20 mg per day, have definite arresting effects in approximately 40 per cent of the older, postmenopausal women with inoperable carcinoma of the breast (128). The particular indication for the use of estrogens is in the presence of soft-tissue metastases, which may regress along with the primary growth for periods of three to six months. Neither estrogen or androgen therapy is curative, nor is there evidence available that the life span is prolonged.

The presently available chemicals showing some effect on neoplasms in man fall into four general classes: (*a*) those attacking some residual physiologically normal function of the cancer cell, such as up-take of iodine by thyroid carcinoma; (*b*) those altering the biochemical substrate of the tumor which still retains relative dependence on such environment, such as the effect of estrogens and androgens in mammary carcinoma, (*c*) the group of bone marrow-lymphoid tissue destructive agents which also influence neoplasms derived from such tissues, such as urethane, arsenic, benzene, and the amine mustards, and (*d*) the agents which injure the vascular supply of the tumors, such as the *S. marcescens* polysaccharide. Further clarification of the mode of action of these compounds is important, and may well produce clues to more effective agents of the same general classes. It is of considerable interest that most of the agents mentioned as having some effect on certain neoplasms in man also have carcinogenic properties Arsenic, roentgen rays and estrogenic compounds are incriminated as carcinogenic in man as well as in animals Urethane produces pulmonary tumors and amine mustards produce both pulmonary tumors and sarcomas at the site of administration in mice and rats (129).

It should be recalled that most carcinogens are also mutagens An important paper by Loveless & Revell (130) divides chemical agents that affect cells into three classes (*a*) general toxic agents, such as the arsenicals, which probably exert their activity through reaction with tissue -SH groups, (*b*) radiomimetic compounds, such as amine mustards and epoxides, whose probable significant reaction is esterification of acid groups, possibly thereby

bringing about cross-linkage between protein or nucleoprotein molecules, and (*c*) colchicine-type compounds which suppress spindle formation in dividing cells but do not induce gene mutation or chromosome breakage Compounds of the second class appear at the present to be most hopeful in the search for specific chemotherapeutic agents for neoplastic diseases.

## CONCLUSION

Generalizations regarding neoplastic diseases are premature, and only broad, tentative patterns can be suggested at present. From the standpoint of etiology and tumor-host relationships, including clinical aspects, cancer must be considered as a group of diseases rather than a single disease entity, if confusion during further essential analysis is to be avoided The basic process by which normal cells become neoplasms, however, may be essentially similar, and probably involves the production of reproducible and transmissible alterations in the genic or cytoplasmic nucleoprotein.

Rapid progress is being achieved in the fundamental knowledge regarding neoplastic diseases. Despite the obvious great difficulties which remain to be surmounted, conservative optimism concerning the eventual solution of the cancer problem, including the discovery of effective therapeutic chemical agents, appears fully justified.

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# DISEASES OF THE REPRODUCTIVE SYSTEM[1]

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## STERILITY

It is appropriate to begin this annual review of the reproductive system with consideration of the involuntary failure of a couple to initiate the reproductive process This phase of the broad subject of human reproduction is designated as sterility and is a fundamental biological and clinical problem of great magnitude Davis (1) expresses the consensus of most investigators in stating that 15 to 20 per cent of all marriages are sterile. Popanoe (2) makes the surprising statement that the chances of childless marriages ending in divorce are 71 out of 100. For many years sterility has been a subject of extensive investigation which has been productive of much understanding and of some practical progress.

The essentials for successful conception may be listed as follows. (*a*) Adequate sperm, (*b*) sperm deposited at the proper time, (*c*) a female genital tract capable of sperm penetration, (*d*) ovulation of a normal ovum, (*e*) the union of ovum and sperm, (*f*) normal tubal migration of the fertilized ovum, and (*g*) successful and normal implantation of the fertilized ovum in the uterus. During the past year progress has been recorded in all of these aspects There is, of course, a good deal of discussion as to the exact specification for a normal sperm count. Hoffman (3) defines the normal as follows: Alkaline reaction, volume of about 3 cc , possessing normal motility, and a count of at least 60 million per cc. There must be only a few pus cells and no red blood cells In 495 patients examined by him as a result of sterile marriages, only 27 per cent met these requirements It is interesting to note that the 60 million count designated by Hoffman (3) is usually the minimum by most other investigators.

Davis (1) is in agreement with most previous opinions when he states that coitus must occur within 24 to 36 hours of ovulation, as the life span of the sperm and egg do not permit fertilization outside of these limits. Failure of sperm to ascend through the female genital tract may be the result of inflammatory conditions within the cervix which usually respond to the ordinary methods of treatment of endocervicitis, or may be due to occlusion of the fallopian tubes. The work of Rubin (4) on tubal occlusion has been outstanding, and to him we owe most of our present knowledge. In his technique of testing tubal patency, insufflation of the fallopian tube is carried out by carbon dioxide under controlled pressure. These pressures are recorded on a kymographic drum He states that kymographic uterotubal insufflation has diagnostic and therapeutic advantages over hysterosalping-

[1] This review covers the period from approximately January, 1947 to January, 1949.

ography. It is a safe procedure, it amply demonstrates tubal patency, clears mucus from the tubes, and at times overcomes spasm It is also useful in the treatment of partial occlusion. The substitution of radio-opaque oils for the carbon dioxide in Rubin's method has been used by many clinicians. Rutherford (5) used this method in 417 cases. Seventy-one per cent of them had relief of tubal occlusion demonstrable by x-ray, and 63 per cent had subsequent pregnancies There was one death in his series as a result of the procedure.

Campos Da Paz (6) reports on 502 cases of hysterosalpingography and considers that it and insufflation are complementary techniques. The advantages of hysterosalpingography are that it offers a valuable means of investigating tubal permeability, especially of localizing the site of obstruction and of demonstrating permanent deformities in the uterine cavity.

The permanently occluded tube has been the subject of surgical attack and numerous techniques have been advanced as a solution to this problem. It is fair to state that none have been successful in a very high percentage of cases. Johnson (7) describes an ingenious "trap door" operation for reestablishing tubal patency In his method carbon dioxide insufflation precedes laparotomy, and the tube is opened on the antimesenteric border at the point of distal crepitation. As the lumen is opened, air and tubal contents gush out. The fashioning of the trap door is left to the ingenuity of the surgeon. It is important that as little dissection as possible be carried out. Johnson (7) reports three cases operated upon by this method with subsequent pregnancies. This method undoubtedly is simple and may appeal to many who have tried other methods and failed

The determination of the ovulation of a normal ovum is a matter which can only be determined by the successful delivery of a normal child It is generally assumed, however, that ova which are ovulated are normal, and there has been much investigation in order to determine the presence or absence of ovulation Perhaps the simplest and most practical method for this is the demonstration of a normal progestational endometrium. Evidence of normal *corpus luteum* formation and hence normal ovulation can also be obtained from a study of sodium pregnanediol excretion. Ferris (8) has used the reaction of the immature rat ovary to the hypodermic injection of the subject's urine for detecting human ovulation. The rat ovary reacts in adequate fashion to the increased urinary excretion of pituitary gonadotropin at the time of ovulation. His findings indicate that the day of ovulation ranges from the sixth to the twentieth, with the postovulatory phase averaging 14.8 days with a range of 11.5 to 20 days By observing the actual time of ovulation for several months, the day of expected ovulation could be predicted with some accuracy in subsequent months. By accurately timing coitus with the expected time of ovulation, Ferris (8) was able to report 50 conceptions occurring in 46 patients

A generally used and practical method for the detection of ovulation is the basal body temperature This method has been reviewed in an able man-

ner by Palmer (9). He believes that the time of ovulation may be determined from the basal body temperature more easily than by any other method. However, it should be remembered that the thermal shift may be an indication but not positive evidence of ovulation. There is abundant animal evidence indicating that a *corpus luteum* formation in which the ovum is imprisoned may still function endocrinologically. Some data indicate this is possible in the human. Palmer (9) suggested that infertility due to the mechanical failure of ovulation may be characterized by a basal body temperature curve in which three to five days are required for the temperature to rise to a level significantly above the low temperature phase. Real ovulation, on the other hand, may be characterized by a curve in which the ovulatory rise is significantly abrupt in 24 hr. In normal menstruating women the basal body temperature falls significantly on the morning of the day in which the menstrual discharge appears It has been shown that the length of the normal menstrual cycle varies directly with the length of the preovulatory phase. The postovulatory phase is usually fairly constant and of about 14 days duration. Occasionally, a patient may exhibit a postovulatory phase of significantly less than 14 days. It is possible that this may be due to a premature degeneration of the *corpus luteum* and may be an explanation of some rare cases of sterility. Occasionally, patients with menometrorrhagia may have a normal basal body temperature associated with irregular bleeding during the high temperature phase of these cycles. This bleeding precedes the menstrual fall of temperature Pregnanediol has been found in the urine during bleeding when the basal body temperature is in the postovulatory phase. It is not demonstrable in the urine during normal menstruation, that is, after the normal menstrual fall of basal body temperature Such bleeding associated with the presence of pregnanediol in the urine or occurring in the high temperature phase of the cycle can be attributed to a faulty function of the *corpus luteum*. Therapeutic measures should be designed to strengthen its function

Along experimental lines the artificial reproduction of the normal hormonal cycle by the substitution of estrogen and progesterone resulted in a basal body temperature curve similar to the normal A close parallel was noted between the excretion of pregnanediol, the development of the *corpus luteum*, and the changes in basal body temperature The ovarian function following the removal of the uterus was also studied by basal body temperature graphs. The general pattern of the curves was typical of normal ovarian activity, as well as the formation of *corpus luteum* This was measured by the urinary output of pregnanediol during a 24 hr. period and was not altered

Attempts to stimulate the nonovulating human ovary with gonadotropic extracts have revealed that various complications exist. One of these appears to be the formation of an antagonist to the hormone administered if the period of therapy is prolonged These antagonists, or antihormones, serve to nullify the physiologic activity of the administered gonadotropin. Leathem & Rakoff (10) used a combination of pituitary extracts and human chorionic

gonadotropin (Synapoidin) in the treatment of 30 women and 4 men for various reproductive disorders. Studies to determine whether this combination of gonadotropins would excite antihormone formation have revealed that these inhibitory substances did not develop in 30 of the 34 cases treated, and generally did not do so in less than five months. In four cases, definite antihormone titers were recorded after five months of therapy. The presence of antihormones could be correlated with the clinical response The failure of the patient to continue to respond to therapy coincided with the time at which antihormones were detected These inhibitory substances tend to disappear in about three months.

The use of the roentgen ray to stimulate ovulation has previously been reported by Kaplan (11). He gives an additional report of 338 cases of amenorrhea and sterility treated by roentgen therapy. Of these, 274 were followed. Favorable results were achieved in 12 unmarried, and 198 married women. In the latter group, after regulation of menstruation, 90 became pregnant and delivered 101 normal children. No ill effects on mother or child were observed.

In recent years considerable attention has been focused on the enzyme hyaluronidase. This belongs to the group of so-called "spreading factors" and is a component of normal spermatic fluid. It is said to be capable of bringing about the dispersion of the follicle cells surrounding the recently ovulated egg, thereby facilitating the process of insemination.

Kurzrok (12) reports 33 pregnancies in 102 selected patients treated by applying 10 to 20 mg. of hyaluronidase to the cervical canal followed by subsequent coitus. However, Tafel *et al.* (13) find a lack of success with hyaluronidase in the treatment of sterility. No pregnancies occurred in their series which could be attributed to its use.

Buxton & Atkinson (14) studied six patients with secondary amenorrhea after a temperature base line had been established. They were given an oral dose of estrogen for two weeks, and this was followed by 10 to 25 mg of progesterone from 7 to 14 days. During the progesterone treatment the estrogen dosage was either eliminated or cut in half. Estrogen may produce a slight depression in basal body temperature, but progesterone produces a definite rise. The postovulatory rise was also maintained in normal women by the injection of chorionic gonadotropin. However, chorionic gonadotropin administered to a castrate after estrogen priming had no effect. Its effect, therefore, is considered to be a result of stimulation of *corpus luteum*.

## MENSTRUATION

The newer concepts of menstruation are succinctly reviewed by Kaiser (15) in an exceedingly well written and valuable article. The arterial system of the endometrium undergoes cyclical changes, with the exception of the basal arterioles which do not participate. As the follicular phase proceeds, the coiled arterioles lengthen and add loops in the lower half of the endometrium After ovulation the loops grow and become much more complex.

The distal portion of the coiled arteries is lost in the menstrual discharge The bulk of the menstrual bleeding is arteriolar, and is controlled by the coiled arterioles There are two basic interpretations of these anatomical findings. The first is a mechanical concept based on an impairment of blood flow as a result of the constriction of the coiled arterioles. This impairment of blood flow is the initiating factor in the chain reaction of menstrual events. The second, a pharmacodynamic concept, stems from the observation that prolonged periods of vasoconstriction are invariable precursors of the other menstrual changes. This constriction of the coiled arterioles is considered to be the initiating factor The growth and differentiation of the coiled arterioles are presumed to render them sensitive to the action of the vasomotor substances Neither of these basic concepts is now acceptable in view of new facts. One of these is the recent observation of arteriovenous anastomoses in human endometrium by Dalgaard (65), and confirmed by Schlegel (66), who suggested that eventually so much of the arterial blood is shunted as to produce capillary ischemia, precipitating the menstrual breakdown Another difficulty with the acceptance of the basic concepts is the explanation of the amenorrhea of early pregnancy, as the coiled arterioles in that vast area of endometrium, distant from the site of implantation, are exceedingly well differentiated Yet bleeding does not usually occur in the pregnant animal Among other objections are the repeated observations that the coiled arterioles found in ovulating menstruation differ considerably from those in anovulatory menstruation Yet clinical bleeding is identical in the two conditions Although no study has been made of this subject, coiled arterioles are not conspicuous in the presence of glandular cystic hyperplasia of the endometrium. Also, there is suggestive evidence that bleeding can occur in rhesus monkeys without any proliferation of the coiled arterioles Lastly, microscopic bleeding can occur in the form of cyclical menstruation in new world monkeys in the absence of any coiled arterioles.

The above observations indicate that the alterations in the coiled arterioles fail to account for much that is known However, before a purely vascular explanation can be entirely abandoned, more information is needed concerning the contraction cones of Daren. These contraction cones are a constriction of the radial arteries in the zone of myometrium adjacent to the endometrium.

A most significant contribution to the understanding of abnormalities of menstruation has recently been made by Phelps (16) as the culmination of a long series of studies in the Department of Obstetrics and Gynecology of the Vanderbilt University Medical School. She states that any given episode of uterine bleeding is influenced by the components, relative strength, and duration of the hormonal stimuli acting prior to application of a current stimulus In other words, the influence of a single course of stimulation by ovarian hormones is not limited to the cycle which that course of stimulation represents. Its influence extends through at least one subsequent cycle, and probably through more than one. This influence upon subsequent cycles is mediated at least in part through the structural changes produced in the

endometrial vascular bed. These changes may be transient or permanent, i.e., carried over into the next cycle. The specific vascular architecture existing at the beginning of any single cycle has an important influence upon the duration of the uterine bleeding in that cycle.

In commenting upon Phelps' paper, Kaiser (15) states, "Phelps has produced evidence that menstrual irregularities are associated with anomalous growth of coiled arterioles in the rhesus This may, therefore, offer further explanation of the relative sterility of women with menstrual irregularities" Phelps' other observation that the effect of hormones is dependent in part, at least upon the previous hormonal history of the subject, as reflected in the state of the coiled arterioles, has very broad implications in the study of sterility. Some of these have been suggested. Further investigation of the association of the coiled arterioles with implantation of the fertilized ovum, especially in the light of this anamnestic vascular phenomena described by Phelps, can be designed to yield results of great experimental and clinical interest.

Brewer & Jones (17), in discussing the *corpus luteum*-endometrium relationships, point out that there is considerable variation at the end of a cycle. They present an histologic study of *corpus luteum*-endometrium relationships in two groups of cases In one there is a *corpus luteum* abnormality consisting of a prolongation of *corpus luteum* function with the characteristic histological changes usually described as irregular shedding of the endometrium. In the second group the *corpus luteum* is normal, and the endometrium responds normally except in small localized areas that failed to respond. Around these areas bleeding occurs The bleeding in this group is not typical of normal menstruation, but rather seems to be from vascular sinuses without much tissue loss or local reaction.

Loeser (18) adds some interesting information on the pharmacodynamic effects of the various hormones on the endometrium Estrogen, in 2 mg. dosages produced vasodilatation. Stilbesterol, 150 mg , produced vasodilatation. Pitocin had no effect. Pituitrin had a prolonged vasoconstrictor effect, as did epinephrine. Progesterone, 100 mg , produced a mild vasodilatation Testosterone, 250 mg , produced vasoconstriction after mild vasodilatory effect

Another interesting physiological observation is Davids' (19) study of tubal motility in relation to the menstrual cycle. Patients with normal ovulatory menstruation exhibit slow, large amplitude contractions of the tubes at the time of ovulation In contrast, the tubal motility pattern in anovulatory patients show no change at the normal time of ovulation, but are similar throughout the cycle. Very interestingly, there were two cases in which estrogen therapy produced obstructive pressures of as much as 200 mm After the estrogen treatment was eliminated, the tubes opened again at normal pressure. This is a finding of considerable importance, and may help to explain many of the cases which are so troublesome in the treatment of sterility. Every gynecologist, from time to time, sees cases in which men-

strual dysfunction might be influenced by emotional factors. Fremont-Smith & Meigs (20) report a well documented case of this kind. There is a ten-year follow-up. The patient, a woman of 29 suffering with menometrorrhagia, was intensely but conservatively treated. Previously, she had been submitted to exploration and other minor surgery. The bleeding stopped, however, three days after a frank discussion of her personal problems with a physician

*Precocious puberty*—The development of precocious puberty is always a subject of interest and concern. According to Hain (21) who presents an informative review of this interesting subject, there are five generally accepted causes of precocious puberty: (*a*) granulosa cell tumor, of which 16 cases have been recorded; (*b*) cerebellar type of precocious puberty, of which there are 17 cases as a result of lesions in the hypothalmus or third ventral; (*c*) adrenal cortical type resulting from tumors of the adrenals; (*d*) gonadal group resulting from tumors or cysts of the ovary; (*e*) group associated with bone cysts and pigmented nevi.

The constitutional type is one in which no adequate cause has been found, and is considered only as the early development of normal puberty. A rare case of precocious puberty is reported by Yerena (22) in which the patient developed menarche at the age of four months.

*Endometrial biopsy.*—In spite of much investigation, the study of the endometrium is still the best index of the functional capacity of the ovary. It is therefore not unusual to find each year a number of new endometrial biopsy instruments such as the one presented by Hannon (23). This is a curette, the head of which contains an ordinary sharp, cutting edge. Below this is a hollow trap to collect the endometrium. Hannon's instrument has the value of simplicity and commends itself for this reason.

In the taking of endometrial biopsies it has been customary to obtain the biopsy as soon as possible after the onset of bleeding. Brewer & Jones (24) point out that the first day of menstruation is the day in which the most variation in endometrial pictures occur, and recommend that endometrial biopsies be taken four to six days before the onset. This is an excellent suggestion and should be of great value in those menstrual anomalies in which the bleeding onset can be accurately predicted. An endometrial picture, however, taken on day one of bleeding is sufficiently accurate to differentiate the types of hormonal activity present in the preceding cycle

*Hormonal treatment*—The use of male hormones in gynecology is still a controversial subject Some well known authorities, such as Hamblen (25), maintain that it has absolutely no place in the treatment of female disorders. The subject is well reviewed by Loeser (26) who states that male hormone is normally excreted in the female urine during the menstrual life and pregnancy. The source is the adrenal cortex and perhaps the ovary. The amount is 42 to 58 I U. daily, in the postmenopausal period, 70 I.U. Each individual has a normal androgen-estrogen-progesterone relationship This determines the individual sex characteristics Laboratory examinations are not now

accurate enough for determining this ratio. Hence, all male hormone therapy is empirical. It has been observed that testosterone propionate in monthly doses of 100 to 200 mg. slowed down the tempo of the normal cyclical development of the endometrium. In doses of 600 mg. monthly the endometrium became atrophic. Discontinuance of male hormone therapy led to a redevelopment of the endometrium and normal cyclical activity. Testosterone acts either on the pituitary release mechanism, or inhibits the formation of the pituitary hormones within the gland. According to the author, intracyclic bleeding usually results from transitory hyperestrinemia In this condition, oral testosterone, 5 mg. daily throughout the intermenstrum, or 25 mg hypodermically four times in the first half of the cycle, is decidedly of value. In the treatment of dysmenorrhea, male hormone has no real place In sterility, excess cervical mucus is due to hyperestrinemia in the absence of cervicitis. One hundred fifty mg. in the first half of the cycle will reduce the secretion, and not prevent ovulation. In frigidity, androgens produce an aphrodisiac reaction when given in large doses. In androgenic suppression of lactation, the treatment starts immediately after delivery. It has the advantage that it does not delay uterine involution as does the estrogen. Puerperal women are very resistant to virilism, hence large doses can be given It must be remembered, however, that androgen therapy is not without disadvantages.

Zondek & Rozin (29) report again on their treatment of amenorrhea following hormonal administration. The basis of this treatment is the injection of a large amount of hormones which temporarily raises the hormonal level, and is then followed by a rapid decline. This decline or hormonal withdrawal is the initiating factor in the development of menstruation. The method recommended is the treatment of amenorrhea by a single dose of estrogen and progesterone The treatment consists of an initial injection of 5 to 10 mg. of estrone, and 50 mg. of progesterone in one injection The results in primary amenorrhea were successful in seven of eight cases. The results in secondary amenorrhea were successful in 40 of 43 cases

*Operative treatment.*—Two interesting reports come from Boston on the use of presacral neurectomy in the treatment of dysmenorrhea. Ingersoll & Meigs (27) report on 111 presacral neurectomies, of which 81 per cent gave complete relief, 4 5 per cent partial relief, and 14 5 per cent no relief Among the operative complications there were two cases of small bowel obstruction. There were no deaths.

Phaneuf (28) reports on 68 presacral operations for dysmenorrhea, of which 59 per cent were satisfactorily cured, 28 per cent improved, 12 unimproved, with one death, anesthetic in nature. Both authors emphasize that the cases must be severe and well screened. It can be seen from these reports that presacral neurectomy involves a certain risk of complications and death, and should not be undertaken lightly.

## THE UTERUS

*Cancer of the cervix.*—Cancer is in the forefront of every clinical discussion of diseases of the reproductive system. During the last decade, great progress has been made in our clinical knowledge of uterine cancer. Much of this stems from the work of Schiller (30) on preinvasive cancer, and the development of smear diagnosis by Papanicolaou (31). The life history of cancer of the cervix is well summarized by Pund *et al* (32) In this work, the term "preinvasive" carcinoma denotes carcinoma which is confined to the natural surfaces and which does not penetrate the underlying stroma. This is not to be used synonymously with "precancerous." In precancerous lesions a cancer cannot be detected but is to be anticipated, as for example, vulval kraurosis and lingual leukoplakia The criteria for the diagnosis of preinvasive cancer are based upon cytologic alterations The nuclei are larger than normal, vesicular and hyperchromatic, of irregular size, and the nuclear-cytoplasmic ratio is increased. Mitotic figures, sometimes bizarre, are readily demonstrable. Differentiation is either absent or incomplete. In the cervix uteri the preinvasive cancer not only involves the external surface, but also extends into the gland of the endocervix. This extension may be mistaken for invasion. However, careful study of several sections will minimize this error

An invasive carcinoma is one in which the epithelium breaks the barriers of the restraining stroma and thereby gains access to vascular channels which may be permeated by neoplastic cells Squamous cell carcinomas of the cervix usually begin in the endocervical canal at the junction of the stratified squamous and columnar epithelia. The source of these cancers is probably the endocervical basal cell whose location corresponds to that of the early cancer Three stages of cervical cancers have been described. (*a*) preinvasive carcinoma, (*b*) covert invasive carcinoma, and (*c*) overt carcinoma

The authors found an incidence of 3 9 per cent of preinvasive carcinoma in a series of 1,200 surgically removed cervices The average age of the patients in whom preinvasive carcinoma had been diagnosed as a result of the pathological study of the surgical specimens was 37 7 years These preinvasive carcinomas were usually asymptomatic, and the lesion was not suspected to be present in the surgically removed cervices After a variable period the preinvasive carcinomas become invasive. Some idea of the latent period may be obtained from the average age of the covert invasive group which was 44 2 years The next step in the progression of the lesion is the development of frank, overt cancer. The average age of the frank, overt cancer group diagnosed by biopsy was 49 years It therefore appears that the majority of cancers of the cervix become obvious only after a period of time averaging five years after the onset of invasion, and eleven years after incipiency. Clinical cancer of the cervix, therefore, means advanced cancer

The advances made in our knowledge of the life history of cancer of the cervix and of its early detection by the Papanicolaou method has naturally

focused attention on this method, and numerous important contributions are continually appearing In a study comparing the accuracy of the vaginal smear and the biopsy in the diagnosis of carcinoma of the cervix, Graham *et al.* (33) present sound reasons why the smear and the biopsy are complementary diagnostic measures in the detection of the early case. In making a comparison of the diagnostic accuracy of the vaginal smear and biopsy in 181 cases of epidermoid carcinoma of the cervix, the first biopsy report was correctly positive in 90 per cent, and the first vaginal smear was correctly positive in 91 per cent. By a combination of the two methods the correct diagnosis was initially obtained in 99 per cent of the entire group

McSweeney (34) mentioned six cases in which the diagnosis was made primarily by the smear, and in reporting 18 cases of carcinoma *in situ*, Foote (35) states that all of the cases were asymptomatic, and a large proportion would have been overlooked without the smear.

From these reports it is very clear that the smear detects some cases of early carcinoma which are not picked up by the first routine biopsy; the biopsy in turn also picks up cases missed by the smear. It is definite, as Graham (33) states, that the two methods are complementary.

The percentage of false positives is given by Kernodle (36) as 2.7 per cent, and by McSweeney (34) as approximately 2 per cent. Ulfelder (37) reports 1.6 per cent false positives. The percentage of false negative smears is given by Graham (33) as 7 7 per cent and by Ulfelder (37) as 12.9 per cent Ayre (38) calls attention to the fact that cytological smears will be more accurate if the squamo-columnar junction is scraped rather than swabbing the canal and taking smears from the vaginal vault.

Foote & Li (35) ask the following question· "What is the incidence of carcinoma of the cervix in the female population at large over the age of 35 years?" Two sources of aid were enlisted in order to secure working figures for this question. Doctor Morton L. Levin of the New York State Division of Cancer Control and Mrs. Ruth Salt of the Department of Statistics at Memorial Hospital independently estimated that in the female population at large one would expect approximately one case of carcinoma of the cervix per 1,500 women over the age of 35. Using this figure as a working basis, acknowledging that not all of these cases would be of the asymptomatic type, one is left with something to ponder. In order to detect one case of carcinoma of the cervix it would theoretically be necessary to make 1,500 smear examinations.

Parrett (39) found 42 positive smears in the first 1,000 consecutive cases studied Twenty-five of these had carcinoma of which four were vulvar, fifteen cervical, five endometrial, and one site unstated. Parrett's experience, as well as others, would indicate a somewhat higher percentage of positive smears than that estimated by Foote.

Cancer of the cervix uteri has always presented a challenge to those interested in pelvic surgery. Wertheim attempted to meet this by developing a very radical surgical attack upon the growth, and his method became the

standard one in Europe, with the exception of a few clinics where the vaginal operation of Schanta was preferred. American surgeons were slow to take up the radical operation, and very few of them developed the same degree of familiarity with it as the continental surgeon. It was, therefore, not hard for the Americans to turn from the radical operation with its high mortality and low salvage, to radium which promised equally good results with little mortality, and the promise of even better results in the future During recent years, however, there has been a stock taking of the results of radiation therapy, and it is generally admitted that radiation results have not continued to improve and are now on a plateau. In addition, there is abundant evidence indicating a high percentage of gland metastases in early cases, which is estimated at 20 to 30 per cent in groups one and two. Moreover, it seems that x-ray and radium have little effect on these metastases, and there are also a certain number of cases which are not sensitive to radium and show radioresistance. As radiation therapy has been advanced to the limits of the tissue resistance, there has been an increasing percentage of complications in the form of rectal and vesical lesions, and these have made the lot of the cancer patients even more difficult. More and more cases are now being reported as cured by the five-year standard which later undergo recurrence between five and ten years. All of these failures of radiation, coupled with the brilliant advances of modern surgery, have naturally led surgeons to re-evaluate the use of surgery in the treatment of cancer of the cervix. It is generally admitted that in certain groups of cases radium produces satisfactory results. The problem now is to learn to pick those cases in which surgery will succeed and radium fail

In England, the Chelsea Hospital for Women was the center of an all-out attack upon cervical cancer. Read (40), one of the contemporary surgeons at Chelsea, presents a most important commentary on the present treatment of cancer of the cervix in the light of the experience of that hospital as represented by the work of Victor Bonney Between 1907 and 1936 Bonney performed 500 consecutive Wertheim operations This was 63 per cent of the cases of cervical cancer presented to him. The series included stages 1, 2, and 3 cases Gland involvement was present in 40 per cent of the cases. His operative mortality was 70 deaths or 14 per cent The cure rate in gland free cases was 50 per cent, and the corrected cure rate in this group was 58 per cent. The cure rate in gland positive cases was 22 per cent, and the corrected cure rate was 23 per cent The overall cure rate was 41 per cent of all cases operated upon. The absolute five-year cure rate of all cases presented was 25 per cent In comparing surgical results with radiological results in 1936, it was seen that radiological results were definitely superior in respect to operative mortality and possibly superior in respect to survival As a result, the policy of the all-out surgical attack was changed to one of selection of those cases which were considered suitable for surgery. The present policy is one of careful screening in the hope of selecting those cases which are unsuitable for radiation, and utilizing surgery in this group. There are seven indications

for surgery: (*a*) radioresistant cases proved either clinically or cytologically, (*b*) columnar cell cancer of the cervix, (*c*) cases complicated by stenosis of the vaginal vault, (*d*) cases associated with large fibroids or with ovarian cysts, (*e*) cases complicated by salpingitis, (*f*) refusal of radiation by the patient, and (*g*) in pregnancy complicating cervical cancer. The mortality rate can be about 3 per cent based on the experience of the author.

Meigs (41) of the Vincent Memorial Hospital, Boston, has been one of the closest of the American students of cancer of the cervix and a leader in the advancement of surgery in the treatment of this disease. From a study of 91 cases which had been carefully selected and operated upon with no mortality, he believes that the results of surgical treatment are now comparable to those achieved by radiation in respect to mortality.

Arneson (42) of St. Louis has been outstanding in the field of radiation in gynecological cancer, and in his paper on radiation and the surgical trend in the treatment of cancer of the cervix he compares the two methods. He admits that the proponents of surgery have proved, in well selected cases, that primary mortality need be no higher for operation than for radiation, and grants that upon the basis of Meigs' work just cited, there is complete justification for exploring again a procedure that was almost entirely abandoned In considering the choice of treatment, it is obvious that findings at bimanual examination are not accurate for determining the probability of lymphatic metastasis, as positive lymph node involvements are found in one-third of the cases in which the parametria are clear Arneson makes a comparison between the work of Bonney and Waterman on the basis of survival rates. Waterman had 579 patients. Using the Schmitz classification there were 442 patients in stages one, two and three. This was 76 per cent of the total number of cases, and there was a five-year survival rate of 43 per cent. In stages one and two there was 34 per cent of the total series with a survival rate of 61 per cent. In stage three there were 245 cases, which was 42 per cent of the total, and a five-year survival rate of 28 per cent. Waterman had in stages one and two between 1936 and 1940, a five-year survival rate of 71 per cent This is compared with Meigs' three-year survival rate of 77 per cent by surgery.

Bonney's experience, as well as that of Meigs and other surgeons, has clearly shown that a certain percentage (Bonney, 23 per cent) of those cases having lymphatic involvement will survive five years It has also been shown that radiation will in all probability not affect those cases with gland metastases In the early groups the results are about the same Mitra (43) states that an analysis of statistics shows that whatever method is followed, the end results are the same in the hands of experts with a small percentage of variation which may be chance variation. The popularity of one method over the other depends not only upon the results obtained but also upon the easy application of the method without harm to the patient. It is generally believed that radiation therapy is much easier to control. But experts are

of the opinion that properly performed radiation therapy is as difficult to learn as the operation itself. It is high time that the fight for supremacy of one method over the others should come to an end. Mitra chose the radical vaginal operation for the following reasons: (*a*) Primary mortality is less. (*b*) Obese patients are handled more easily. (*c*) Complications in the nature of fistulas are less. (*d*) End results are practically the same (*e*) The greatest handicap of the radical vaginal operation is that cancer-affected lymph nodes cannot be removed. However, almost the same end results have been found in his series of vaginal operations without removal of the glands. The logical conclusion naturally follows that an operation for cancer of the cervix entails the most radical possible excision of the parametrial and paravaginal cuff including also a wide cuff of the vagina. (*f*) The percentage of recurrence does not differ greatly after the two methods of operation, abdominal and vaginal. (*g*) Surgeons can remove a greater amount of parametrial, paravaginal, paravesical and pararectal tissue by the vaginal route than by the abdominal route. In Mitra's series, parametrium has been removed to the extent of about two and one-half inches from each side. Lastly (*h*) the vaginal operation facilitates the introduction of radium in the parametrial tissue. The following results were obtained: stage one, 61.5 per cent cures; stage two, 44 per cent cures, stage three, 15.6 per cent cures Using radiotherapy during the same period, stage one, 66 per cent cures; stage two 31 per cent cures; stage three, 12.6 per cent cures

Bowins & Fricke (44) report the following five-year cures with radiation therapy of carcinoma of the cervix: Stage one, 58.8 per cent; stage two, 65.3 per cent, stage three, 33.7 per cent; stage four, 16 5 per cent. Kimbrough & Muckle (45) report the cases from the University of Pennsylvania from 1936 to 1941, as shown in TABLE I.

TABLE I

RADIATION THERAPY OF CARCINOMA OF THE CERVIX

| Stage | Total | 5-Year Salvage | Per Cent |
|---|---|---|---|
| I | 7 | 6 | 85 7 |
| II | 38 | 18 | 47 3 |
| III | 66 | 12 | 18 2 |
| IV | 19 | 0 | 0 |
| | 130 | 36 | 27.6 |

Diddle & Bennett (46) present an interesting compilation of results of the Metropolitan Hospitals in Dallas, Texas, from the period 1936 to 1946 In those patients subject to follow-up, the survival rates shown in TABLE II were obtained

One of the great drawbacks to radiation therapy has been the intestinal changes secondary to radiation of pelvic malignancy. Often these are so serious that they incapacitate the patient more than the primary disease.

Maas (47) reviewed 600 cases submitted to radiation therapy. Five-hundred-twenty-three of these suffered from radiation sickness, and 70 cases developed permanent rectal changes. Of these 48 developed rectal stenosis Thirteen other cases developed recto-vaginal fistula. Secondary carcinoma of the bowel occurred in 10 instances.

Johnson & Jacox (48) also directs attention to rectal hemorrhages following irradiation for carcinoma of the cervix and report an interesting case requiring colostomy.

In pelvic cancer, a major cause of the high death rate is failure to make a diagnosis while the treatment is still favorable. Most authorities are agreed that progress in early diagnosis is the best hope for improvement in end results As a result of this viewpoint there has been organized in Philadelphia a committee to study the subject of pelvic cancer delay. A report of its activities is given by Howson (49) Between November 1, 1945 and January 1, 1947, some 455 living patients with pelvic cancer were investigated In

TABLE II

SURVIVAL RATES FOLLOWING RADIATION THERAPY OF CARCINOMA OF THE CERVIX

| Stage | Total | Living | Per Cent |
|---|---|---|---|
| I | 21 | 17 | 81 |
| II | 50 | 32 | 64 |
| III | 105 | 31 | 29 5 |
| IV | 62 | 3 | 4 8 |
| Unclassified | 329 | 106 | 32 2 |

145 cases, or 31 8 per cent, there had been no delay from the onset of symptoms to the consultation with the physician. In the remaining 310, or 68 1 per cent of the cases demonstrated, there was a lapse of one or more months from the time the symptoms were first noted until the correct diagnosis was made and adequate treatment instituted Of these 310 cases showing a delay, it was found that the patient alone was responsible for 197, or 63.6 per cent, and the physician alone was at fault in 76, or 24 5 per cent of the cases. In 37, or 12 per cent, of the cases the patient and physician were both equally dilatory. These figures demonstrate the role of the physician in pelvic cancer delay.

Diddle & Bennett (46) also discussed the question of pelvic cancer delay In their series there is a delay chargeable to the patient of 6.4 months and to the doctor of one month.

In spite of all that has been done in the treatment of cancer, a vast majority of the patients with cancer of the cervix die. The treatment of an inoperable case or a case in the terminal stages of the disease is of major importance. This has been recognized by Memorial Hospital of New York, and they have imported Alexander Brunschwig of Chicago, one of the most radical abdominal surgeons in the world, for an all-out surgical attack on cancer of the pelvis in the hope of doing something for this group of sufferers. Brunschwig (50) points out that cervical cancer remains relatively localized for prolonged periods, and the lesion is therefore favorable for operation. He recommends a radical operation more extensive than anything hitherto described for the so-called hopeless case (51). It is a total excision of all the pelvic viscera. It appears to be among the most radical abdominal operations that have been carried out with some measure of consistency. The operation is done in two stages: (*a*) the abdominal stage in which the bowel is divided and brought out as a colostomy, then pelvic viscera are dissected free and the ureters are implanted into the bowel, and (*b*) the perineal stage in which the incision is made circumcising the vulva and anus and removing the pelvic viscera *en bloc*. Twenty-two patients have been operated on, and five patients died. It is to be remembered that all of these patients were considered to be in the terminal stage of the disease Aside from the immediate effects of palliation, the following interesting point is raised by this procedure It would appear that once carcinoma of the pelvis cannot be controlled by a relatively conservative method, that is, irradiation alone or in combination with some standard type of operation, radical surgery of this type may have something to offer and might well be considered curable early in the stages of recurrence rather than be postponed until it has spread extensively throughout the pelvis.

*Cancer of the body*.—Cancer of the body of the uterus presents a variable clinical picture which must be considered in every differential diagnosis of uterine bleeding Carcinoma of the body of the uterus arises from the endometrium During reproductive life this tissue is constantly changing under the influence of hormonal stimuli After reproductive life an added stimulus may come from injected estrogen It is to be expected, therefore, that these stimuli may have a role in the development of endometrial cancer. Much study has been devoted to this phase of the picture

Gusberg (52) describes a pattern of adenomatous hyperplasia of the endometrium which bears a constant relation to estrogen stimulation in both benign and malignant tissues The data presented concerning this estrogen-tumor relationship is in four related groups: First, in granulosa and theca cell tumors, Hodgsen *et al.* (67) found corpus carcinoma in 21 per cent of 38 postmenopausal women with granulosa cell tumors In nine cases studied by Gusberg, one had corpus carcinoma In the second category one finds hyperplasia of the endometrium following prolonged estrogen administration. Twenty human endometria were studied in the various degrees of hyper-

plasia fall

These metaplastic areas ... The response of the endometrium was more related to the duration of treatment than to the amount of estrogen administered. In the third category are to be found the ... following ... endocrine ... possess carcinogenic properties in the h... strong point is the widespread use of estrogens and the lack of any precise evidence of a malignancy which has been produced ... administration. Case reports were ... adenoca... ti... the medication and the neopl... of the well known character of this tumor to remain local for relatively long periods of time; however, these histories are suggestive of an etiological relationship Lastly, the writer studied the endocrine background of patients with *corpus carcinoma* and noted deviations suggesting an abnormality of the internal secretions ... creased ... In s... shou... have been given f... time, ... this is one ... evidence that incr...

One of the grea... the role of estrogens in carcinoma of the body of the uterus is the difficulty of different... from the malignant Th... ing contribution by N... of lesions which have ... The lesions are different from the ord... benign swiss cheese hyperplasia which has no tendency to malignant transformation. The material forming the immediate basis for this study consists of a group of cases which show atypical hyperplastic changes which might readily be mistaken for adenocarcinoma, and which, as a matter of fact were actually so diagnosed in many instances. In the study of any large number of hyperplastic endometria one will encounter every possible histologic gradation between the frankly benign and the obviously malignant The fact that the histologic transition between the benign and the malignant is marked by almost insensible tran... not, of course, mean that the... of a benign to a malign... irreversible somatic mu... this a benign into a malignant ... the beginning cannot as a rule ... now available.

... treatment of cancer of the body of the uterus is among the most satisfactory of that of any internal organ. Here again we have the conflict

between the claims of the surgeons and the radiotherapists. In this area more agreement has been reached than concerning cancer of the cervix. Most authorities on the basis of rather good evidence believe that radiation followed by surgery is the treatment of choice. However, Speert & Peightal (54) of the Roosevelt Hospital in New York make an evaluation of adjunctive radiotherapy in the surgical treatment of endometrial carcinoma, and show an analysis of 157 cases with no benefit from preoperative radiation with intrauterine radium. They report a five-year cure rate of 85 per cent by hysterectomy alone in early cases, with a cure rate of 91 per cent in histologic grade one cases.

The technique for the radium application for cancer of the body of the uterus is of course important and has been a subject of considerable discussion Arneson *et al.* (55) discuss this technical feature In 1938 the method of radium treatment was changed by these authors from one employing intrauterine tandems to a technique employing multiple capsules of radium. Radiation is now preceded by external x-ray. Cases suited to hysterectomy are given both x-ray and radium. Residual cancer was found after 77 per cent of the tandem applications in specimens removed at hysterectomy operations and in only 26 per cent after the multiple capsules had been used.

*Endometriosis.*—The discussion of the etiology of endometriosis continues. Meigs (56) presents a clinical study indicating that endometriosis is definitely related to childbearing, and its incidence is increased in those patients who marry late and bear children late in life. The instance of endometriosis in private patients is greater than on the ward service He states that this is a factor of considerable social importance. Da Costa (57) cites some odd instances of aberrant endometriosis. One patient presented hard, painful nodules in the inner aspects of the thighs, becoming reddish and swollen before menstruation, and some of these actually bled. These nodules showed scarlike changes following mestruation, and new ones soon developed Similar lesions later appeared in the lower mammary grooves in the pectoral regions and in the axillary folds A biopsy from the thigh revealed typical endometrial tissue The histogenesis is discussed in relation to the metastatic theory of Halban and Sampson and the embryonal rest theory of Robert Meyer. The latter seems the most likely explanation of this case Either the Meyer-Iwanoff or the Sampson regurgitation theory may be used to explain the development of endometriosis to the intestinal tract This is a fairly uncommon lesion, but does occur sufficiently often to be noted by practically all surgeons Its recognition and treatment, therefore, is of practical importance

Schmitz & Grossbard (58) present a case of endometriosis of the perineum. This is extremely unusual. Previous case reports indicate that it occurs primarily following operative procedures performed at the time of delivery. Their patient was a 23-year-old Negro who had a normal spontaneous delivery and a left mediolateral episiotomy For years the scar of the episiotomy

was painful and swollen with the periods and showed typical lesions of endometriosis.

Sutler (59) states that endometriosis occurs in 10 to 22 per cent of women requiring an abdominal operation, and in 8 to 15 per cent of all women during active menstrual life. In his series the intestinal tract was involved in 35 cases, the appendix was involved in 25, the ileum in one, and the rectosigmoid in 9.

McGuff (60) throws further light on the involvement of the intestinal tract by endometriosis. The differential diagnosis between endometriosis and cancer of the sigmoid at times is difficult. It is important to remember that endometriosis invades the bowel from the serosa inward, while cancer invades from the mucosa outward. A smooth mucosa eliminates the possibility of cancer. In endometriosis of the bowel, the average age of the patient was 39 years Three-fourths of the patients were sterile. There were four cases of complete obstruction, six cases of partial obstruction and six cases showing chronic intermittent obstruction. Microscopic endometriosis was found in all layers of the bowel. Surgical treatment of these cases produces complete relief. Most surgeons are now beginning to recognize that endometriosis is a long continued disease with frequent remissions and affecting a large percentage of the female population. A vast majority of the cases of endometriosis require no treatment, and treatment should only be instituted when necessitated by the symptoms. The malignant potential of the lesion is low, and it is therefore of interest that a case of adenocarcinoma arising in an endometrial cyst of the ovary was reported by Miller (61). This seems to be a very clear cut case and is a very rare condition The first case was reported by Sampson, and according to Novak (68), there are only five others reported.

Meigs (56), Payne (62) & Counseller (63) all go on record again as favoring conservative tendency in surgical treatement of endometriosis Schmitz & Town (64) reviewed 130 cases treated with the aim of preserving ovarian function and permitting childbearing The average age in their series was 32 The older the patient the more radical the treatment The surgical group of 57 cases was by far the most satisfactory. Seventeen of 29 patients given castration doses of x-ray received complete relief Six of 15 patients given oral testosterone were free of symptoms as long as it was continued. Eight more could carry on with residual symptoms

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the following manner: 2½ cc. of filtered first morning urine are injected in the dorsal lymph sac of four frogs. The frogs are placed in separate containers. One hour after injection a drop of urine is obtained from the frog by placing the opening of the cloaca upon a clean glass slide. Slight pressure is then applied to the ventral surface to obtain the urine Spermatozoa are readily identified by low power microscopic examination. Urine specimens from the frogs are examined 1, 2, 4 and 8 hr. after injection. If *vast quantities of* spermatozoa are present the test is considered to be positive; if no spermatozoa are present the test is considered to be negative. Occasionally only one or two spermatozoa are present on the entire slide. This is not considered a positive test, since spermatozoa occasionally come loose from the Sertoli's cells and appear in the urine.

A four day interval is allowed to elapse before reusing the frogs after a positive test. However, the frog may be used the next day following a negatve test.

Two hundred and forty-eight tests have been studied by Job (7) using this technique. Four of the specimens killed all the frogs. There were six false negative results and five false positive results. The accuracy, therefore, was 95.0 per cent.

Although more experience with this test will be necessary before final evaluation as to its accuracy can be made, the several advantages it possesses are self-evident. It is already apparent that this test is as accurate as other tests now in use, and it has the additional advantage of being inexpensive and rapid. The fact that the test is not dependable in the latter part of pregnancy would seem unimportant from the practical viewpoint

*Toxemia.*—It is now generally accepted that the hypertensive aspect of the toxemias is related to vasospasm The etiological agent or agents responsible for this phenomenon remain obscure, although diligent search for pressor substance has been carried out. No excess renin has been found in the kidney and no renin or renin-like substance in the placenta.

During the past few years new pharmacologic tools have been discovered and used for medical research in the field of hypertensive disease. These tools are three in number. Tetraethylammonium chloride (TEAC), which blocks the autonomic nervous system at the ganglionic level (8, 9), [illegible] which blocks the preganglionic fibers, and veratrum viride [illegible] these

eclamptics and 5 eclamptics were given 400 mg. of TEAC intravenously. In the nonpregnant individuals there was a slight fall in blood pressure, while those near term exhibited a marked fall to mean levels of 55 to 65 mm of mercury. Twenty-four hours postpartum these latter patients showed a rise in TEAC floors to the normal nonpregnant level. The resultant fall in the toxemic patients was negligible. This would seem to substantiate the current concept that toxemia is of humoral origin. This is not, however, a suitable drug for the treatment of toxemia since its action is of short duration and relatively unpredictable.

Conduction anesthesia, and in particular spinal anesthesia, gives a much more predictable and profound fall in blood pressure in cases of toxemia. Furthermore, the use of continuous techniques allows for prolongation of treatment.

From Memphis, Tennessee, comes a sample case report of a patient managed for more than 60 hr. with two types of conduction block (12). Hingson (13) reports the histories of 74 eclamptic patients treated with various types of block anesthesia. There was an infant mortality rate of 18 4 per cent with three maternal deaths. All of these patients had marked reduction in blood pressure, but it must be emphasized that block anesthesia is a powerful remedy to be used only by the experienced operator.

The good results achieved by the Cincinnati group in the treatment of toxemia with veratrum viride are well known (14, 15, 16). It is remarkable that while the standard 0.2 cc. intravenous dose does not affect the blood pressure of the nonpregnant individual, it invariably invokes a marked fall in the pre-eclamptic patient.

The results with various drugs are not yet clearly understood, but the possible results of future study in clarifying the physiology of toxemia are self-evident

## Labor

*Natural childbirth*—The concept of childbirth without anesthesia and with maximum maternal co-operation is not new (17). Prior to Simpson this was all that existed, and as short a time as 15 years ago no pain relief or anesthesia was administered in normal labor at one of the world's greatest maternity hospitals. The cry and turmoil of the labor room was disconcerting, but the joy of the mother with her newborn child seemed undiminished. These mothers neither knew nor expected more than this Today, in America at least, there is a vast difference. Adequate and safe pain relief is available to all who desire it. To a large extent, fear of childbirth as a pain-racked ordeal is beginning to disappear. With the vanishing of old fears it is but natural that a desire should arise in some women to perform what appears as a perfectly physiologic act in a physiological manner. Under the impetus of Read in England (18, 19) and numerous lay articles in popular magazines and college alumni journals there is a growing patient demand for so-called natural childbirth. Unfortunately this movement has developed a certain

the following manner. $2\frac{1}{2}$ cc of filtered first morning urine are injected in the dorsal lymph sac of four frogs. The frogs are placed in separate containers. One hour after injection a drop of urine is obtained from the frog by placing the opening of the cloaca upon a clean glass slide. Slight pressure is then applied to the ventral surface to obtain the urine Spermatozoa are readily identified by low power microscopic examination. Urine specimens from the frogs are examined 1, 2, 4 and 8 hr. after injection. If vast quantities of spermatozoa are present the test is considered to be positive; if no spermatozoa are present the test is considered to be negative. Occasionally only one or two spermatozoa are present on the entire slide. This is not considered a positive test, since spermatozoa occasionally come loose from the Sertoli's cells and appear in the urine.

A four day interval is allowed to elapse before reusing the frogs after a positive test. However, the frog may be used the next day following a negative test.

Two hundred and forty-eight tests have been studied by Job (7) using this technique. Four of the specimens killed all the frogs. There were six false negative results and five false positive results. The accuracy, therefore, was 95.6 per cent.

Although more experience with this test will be necessary before final evaluation as to its accuracy can be made, the several advantages it possesses are self-evident. It is already apparent that this test is as accurate as other tests now in use, and it has the additional advantage of being inexpensive and rapid. The fact that the test is not dependable in the latter part of pregnancy would seem unimportant from the practical viewpoint.

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During the past few years new pharmacologic tools have been discovered and used for medical research in the field of hypertensive disease. These tools are three in number. Tetraethylammonium chloride (TEAC), which blocks the autonomic nervous system at the ganglionic level (8, 9), spinal anesthesia which blocks the preganglionic fibers, and veratrum viride the site of action of which is unknown (10). As might be anticipated, these drugs have opened new avenues of approach to the study of toxemias of pregnancy.

When TEAC is given intravenously in standard dosage to patients with hypertensive disease of neurogenic origin, or to normal individuals, there is a fall in blood pressure to a level called floor (11). This is supposed to represent that portion of the blood pressure maintained by the humoral content and the intrinsic tone of the vessel walls. In an effort to assay the relative importance of the humoral and neurogenic factors in the toxemias of pregnancy, 10 normal nonpregnant women, 10 women at term, 18 pre-

be given with little impairment of fetal respiration, provided a terminal block anesthesia, rather than general anesthesia is employed Thus, the single injection technique of relatively small doses of an anesthetic agent, as embodied in saddle block, would seem to provide a nearly ideal solution for certain types of labor. Nearly all the local anesthetic agents have been used and may be prepared as shown in TABLE I (26). Inasmuch as the anesthetic is of short duration it is necessary to time its administration properly. In all probability, delivery should be anticipated within an hour following the onset of anesthesia. With the patient in a sitting position a spinal puncture is made at the level of the fourth interspace. A short bevel 22 to 28 gauge needle is commonly used. When free flow of spinal fluid is obtained a Luer-Lok syringe containing the properly prepared solution is attached to the needle, aspiration of one-tenth of a cc. of spinal fluid carried out and the solution rapidly injected. At the end of 10 sec. the needle is removed and at exactly the proper time indicated in the table below the patient is placed flat on her back with a pillow under her head, to keep the neck sharply flexed. The procedure should be timed so that it is carried out between uterine contractions.

TABLE I

Preparation of Anesthetic Agents Used*

| Drug | Dose | Method of Preparation | Time Sitting Up |
|---|---|---|---|
| 1 (a) Nupercaine (buffered) 1:200 sol. | 2 5 mg. | Draw up 2 cc. of 10 per cent glucose, then 2 cc of Nupercaine. Mix. Discard all but 1 cc. | 30 sec. |
| (b) Nupercaine (unbuffered) 2 5 mg cc in 5 per cent glucose | | Draw up 1 cc of prepared solution Use as such. | |
| 2 Pontocaine 1 per cent sol. | 5 mg. | Draw up 2 cc 10 per cent glucose, then 2 cc. of Pontocaine. Mix. Discard all but 1 cc. | 30 sec. |
| 3 Novocaine (Procaine) | 50 mg | Draw up 3 cc 10 per cent glucose, then 1 cc of Novocaine Mix Discard all but 1 cc. | 35 sec |
| 4 Metycaine 10 per cent sol | 33 mg | Draw up 2 cc. of 10 per cent glucose, then 1 cc of Metycaine. Mix Discard all but 1 cc. | 35 sec |

* From Andros *et al* (26).

missionary aspect of fanaticism which makes difficult the separation of fact from fiction. The achievement of a hundred years' work in obstetrical pain relief cannot be lightly cast aside as injurious, or psychologically detrimental to an enlightened womankind. Anesthesia has not only an humanitarian end, but makes possible gentle, careful, and meticulous work by the surgeon and obstetrician as well. This fact in itself should lead to lower infant mortality rates.

Goodrich & Thoms (20, 21) have attempted to apply methods of natural childbirth to the large teaching clinic at New Haven. They have selected every third patient arbitrarily for one group to be so treated, and derived another from the patient's personal choice Adequate prenatal instruction and labor room support have been furnished to these patients. Eighty-nine and five-tenths per cent of the voluntary group appear in the excellent and good categories with only a 10 per cent failure rate; 76 8 per cent of the arbitrarily selected group are classified as excellent or good with a 23 per cent failure. The vast majority of these mothers would have their babies by this method again by choice. The low infant mortality rate and incidence of complications attest the normalcy of these patients. Unfortunately, there appears no control group using other methods of pain relief.

The value of prenatal instruction to patients cannot be denied. The late Henricus J. Stander, commenting on the Read technique in regard to patient instruction said, "This is just what all good obstetricians have been doing right along." On the other hand, the benefits of prenatal exercise have been subjected to serious question by Rodway (22) in well controlled series. This author was unable to find any benefit derived from supervised exercise either in regard to the completion of labor or to the relief of pain.

Whether women who have had previous knowledge of childbirth need or desire pain relief is a moot question A group of parous women physicians in England, questioned on this point as regards their own personal experiences, felt not only a desire for pain relief but for more relief than had been given them (23).

The truth seems elusive but certainly never can be gained so long as opinion replaces scientific observation. The Yale group have made a step in the right direction. The emphasis on natural childbirth has brought to the fore the importance of the psychologic aspects in labor. This in itself is a contribution. In our own clinic, the hard bed and the cold white walls of the labor room have been replaced by cheerful furniture, harmonious colors, and pictures. Music and even television have been tried as psychosomatic supports to the woman in labor It becomes apparent that deep oblivion is not enough nor always desirable

*Low dosage hyperbaric spinal anesthesia (saddle block).*—This type of spinal anesthesia was originally advocated by Pitkin (24). More recently, Adriani and his co-workers (25) have revitalized interest in this subject. This form of anesthesia has become one of the most popular in the United States today. It has been repeatedly demonstrated that very adequate sedation can

used to block those nerves innervating the cervix, vagina and perineum. Flowers (32) has reported that this type of anesthetic is excellent for the seriously handicapped patient and for those to whom caudal cannot be given. It would also seem to have some use in Cesarean section. It is, however, too early to make any definite statement as to the results achievable with lumbar peridural anesthesia.

*Uterine inertia*.—Interest has been revived in the possibility of treating inertia with small repeated doses of pituitary extract (33, 34). One-half to one minim injected intramuscularly every 30 min. appears safe if the five following contraindications are absent: (*a*) Cephalo-pelvic disproportion, including malpresentations; (*b*) multiparity greater than four; (*c*) maternal age over 35; (*d*) fetal weight over 4,000 gm.; (*e*) previous Cesarean section This method of therapy fails to bring about full dilatation of the cervix and/or descent of the head to such a position so that easy delivery is possible in 11 7 per cent of cases (35). Factors contributing to the failure rate are long duration of labor prior to treatment, the presence of intrapartum fever, and high station of the head when treatment was first instituted. The uncorrected fetal mortality in successfully treated cases was 4.5 per cent. However, failure of pituitary extraction stimulation to make the fetus easily deliverable resulted in an uncorrected mortality of 21.2 per cent. In an effort to provide a safer and more physiological method of giving this drug, high dilution intravenous drip was tried, using pituitary extract in dilution of 1:1500 in 5 per cent glucose. This solution was administered intravenously by drip at the rate of one-half minim of the extract per 30 min While the failure rate with this method was not improved, excellent fetal mortality results were obtained in both the successful and unsuccessful groups. The increase in amplitude and frequency of uterine contractions seemed to be more physiological and were certainly more controllable There was immediate cessation of contractions when the drip was discontinued Almost simultaneously Theobald (36) in England employed high dilution intravenous drip pituitary extract in the induction of labor and the stimulation of uterine pain in cases of uterine inertia. It must be remembered that the use of pituitary drip in labor and for the induction of labor is in its experimental stages To employ this method in labor following Cesarean section, or in the face of floating head, or malposition, is certainly not advisable Exact knowledge as to pelvic size by x-ray prior to the administration of the drip should be obtained in all cases.

*Placenta previa*.—While the maternal mortality has been appreciably reduced in the past decade by means of whole blood transfusion, fetal mortality in placenta previa remains in the neighborhood of 30 to 40 per cent, largely because of prematurity

Among 105 cases of placenta previa seen during the last 11 years, 41 were treated in an expectant manner (37). The fetal mortality in the entire group was 28 per cent. However, among 74 patients who were successfully carried to term or who did not have their initial bleeding until the child was near

Any physician who observes deliveries under any of the conduction anesthesias cannot help but be impressed with the benefits derived by the fetus. In a carefully controlled series of 719 deliveries (26) 95 per cent of the infants breathed spontaneously in less than 1 min. after delivery. In only 1 per cent was respiration delayed over 3 min. The time of the initial infant cry was impressively short also. In the same series, the uncorrected infant mortality rate was 0.85 per cent.

Fall in blood pressure is a possible complication of any spinal anesthesia and should be watched for and diligently combated. In the above mentioned series a maximum fall of systolic pressure of 20 mm. of mercury or greater occurred in 26 per cent of the cases. The mean drop was 14.8 mm. One of the most serious objections to this type of anesthesia is postpartum headache. The incidence was 14.5 per cent in this series with 10.2 per cent having mild headache; 3.8 per cent moderate and 0.8 per cent severe. These figures agree in general with those occurring in our own clinic It would seem from the work of Frankson (27) that spinal headache is due to a continual leakage of fluid through the puncture hole in the dura. Small 28 gauge spinal needles may make this continued leakage unlikely. Striking results in the treatment of headache have been reported by Ahern (28) with the injection of saline into the spinal canal and by Rice (29) with the injection of saline into the epidural space Andros (26) reports that 72.2 per cent of his cases received excellent pain relief, and in 20 per cent relief was adequate, indicating mild discomfort with delivery and/or minor postpartum headache or urinary difficulty. The results were poor in 6 4 per cent. In the current enthusiasm for this type of anesthesia it should not be forgotten that, although rarely, nerve damage does occur.

*Lumbar peridural anesthesia.*—Peridural anesthesia or block implies that the local anesthetic drug is inserted along some point of the spinal column and paralyzes nerve trunks at, or directly beyond, their point of egress from the dura This type of anesthesia differs from spinal in that medication does not enter the spinal canal. As Cleland (30) points out, this materially reduces the hazard of nerve damage and the danger of profound systemic reaction is somewhat lessened. Furthermore, it is possible with this type of anesthesia to produce sensory without motor impairment. Lumbar epidural block requires more of the anesthetic agent than does spinal but considerably less than caudal. Because of the localized point of application, segmental anesthesia can be provided wherever desired The technique as originally employed by Graffagnino (31) was hazardous because of the danger of massive spinal anesthesia, and was somewhat difficult of performance. Modifications of the original technique have been reported (32) which have somewhat obviated these difficulties.

Cleland (30) has recommended that caudal and lumbar peridural block be employed during labor. During the early part of labor the lumbar peridural is used to block the pain fibers from the uterus through the eleventh and twelfth thoracic nerves. As the head descends the caudal anesthetic is

out, for only in this manner can an intelligent plan of delivery be achieved In case of low implantation or marginal placenta previa, especially in multipara, simple rupture of the membranes may be sufficient. *In all primipara* and in multipara with marginal or complete placenta previa Cesarean section is the method of delivery of choice.

From an analysis of placenta previa at The Johns Hopkins Hospital it would appear that the concept is correct that the initial hemorrhage is rarely, *if ever, fatal in the absence of vaginal manipulation, and that subsequent* hemorrhage is rarely, if ever, fatal in the absence of vaginal examination provided the hemoglobin is normal at the onset of the hemorrhage. In 304 cases (41) in no single instance was an initial hemorrhage fatal except after

at intervals of about a week, and fainted following the last. Even in this neglected, exsanguinated woman who received no transfusion, death did not occur until intercervical manipulation precipitated further bleeding and shock. Provided the patient is in the hands of an obstetrician of seasoned judgment, provided she is in a modern hospital with an alert staff and a good blood bank, and provided the patient's blood loss and hemoglobin are vigilantly followed, it becomes apparent that the expectant treatment of placenta previa will yield a marked reduction in the currently high infant mortality rate in cases of placenta previa

## THE NEWBORN INFANT

*Retrolental fibroplasia.*—Since the first description of retrolental fibroplasia in 1942 (42) great interest has been shown in this disease, which can result in total blindness in premature infants.

Terry felt that the basis of the disease lay in the development of embryonic connective tissue in a persistent vasculosa lentis. He attempted, without success, to reproduce the disease in animals (43) Reese & Payne (44) differed from Terry in that they thought the disease was a congenital persistence of hyperplastic remnants of the premature vitreous Krause (45) also thought the disease was congenital in that the essential lesion was a prenatal abnormality of the cerebral and retinal neuro-ectoderm

Owens (46) discounted the congenital etiology of the disease, for in an examination of 214 premature infants whose birth weight was 2,000 gm or less, he was able to observe the course and development of this syndrome in nine instances Retrolental fibroplasia developed in these infants between two and five months of age, at which time all visible remnants of the hyaloid system had disappeared. Their initially normal fundus picture was replaced by dilatation of the retinal vessels, followed by profuse retinal exudation, retinal detachment and the formation of a retrolental membrane.

*Rubella*—The original papers of Gregg (47) and Swan (48) which called attention to certain congenital defects in infants born of mothers who con-

term size, the fetal mortality was only 10 per cent. This compares with the rate of 68 per cent in the 31 patients who went into labor spontaneously or in whom pregnancy was terminated before the child attained a size of 2,500 gm. Williams (37) states that if the patient is at term or the fetus viable the method of delivery may be selected according to the patient's condition. When the child is too small to survive and labor has not begun, expectant treatment is advisable. A careful vaginal examination should be carried out to rule out rupture of cervical varices or cervical tumor. Under no circumstance should the cervical canal be entered. With adequate transfusion to replace the blood loss the patient may be kept under observation, preferably in the hospital, although some have been allowed to go home with strict orders to abstain from intercourse, to allow no vaginal examinations, and to return at the first sign of vaginal bleeding. Forty-one patients were kept under observation from two days to three months in an effort to obtain a viable child; 14 had two or more periods of hospitalization for recurrent bleeding. There was no maternal mortality and the infant death rate was 12 per cent (37).

In view of the better infant mortality, the expectant treatment of placenta previa would seem to be of merit. This concept represents a definite departure from the old accepted treatment of placenta previa. Where formerly it was advised that pregnancy be terminated as soon as the diagnosis was made, a waiting policy is now recommended in certain favorable cases, with very premature infants. This concept stems from two independently published papers (31, 32, 38, 39) and is based on the point that the first hemorrhage in placenta previa is never fatal in the absence of vaginal manipulation and subsequent hemorrhages are not fatal in the absence of vaginal manipulations provided that the hemoglobin was normal at the onset of the hemorrhage. Therefore, if adequate blood replacement therapy is carried out, the expectant treatment will yield larger and more mature infants By way of supporting this, Macafee (38) points out that in the last 47 cases treated in a large measure expectantly the average weight of the infants was 6 pounds 12 ounces, while in the first 47 cases of his series which were largely treated at the initial hemorrhage, the average infant weight was 5 pounds 2 ounces. Moreover, the fetal mortality was 47 per cent in the early series against 6 per cent in the last 47 cases.

Macafee (40) now reports 191 cases treated expectantly with a fetal loss of 22 per cent and one maternal death. In support of his advocacy of this departure from the old policy of treatment he stated that *(a)* severe initial hemorrhage rarely occurs aside from vaginal manipulation; *(b)* some patients having moderately severe bleeding at 30 to 34 weeks can later be palpated inside the os without the bleeding because of infarction of the placenta, and *(c)* repeated hemorrhages have occurred in hospitals without embarrassment to either mother or infant providing the blood was replaced.

Macafee (40) recommends the postponement of vaginal examination until the termination of the expectant treatment It should then be carried

While Swan's paper is suggestive that rubella may cause stillbirth it by no means proves the point. A good deal of further investigation will be necessary. The high incidence of congenital malformation apparent when maternal rubella occurs during the first trimester of pregnancy would seem to indicate serious consideration of interruption, provided the diagnosis of rubella has been confirmed by a competent physician.

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tracted rubella in the first trimester of pregnancy has stimulated intensive investigations into the effects of all virus diseases on the fetus in utero.

In an effort to determine the extent of abnormalities resulting from maternal rubella during pregnancy Patrick (49) sent questionnaires to 9,674 mothers of children attending state primary schools, denominational primary schools, opportunity schools and grade schools, the school for the blind and deaf, and private schools and institutions. Of the questionnaires, 7,822 were returned, which approximated one-third of the children in Queensland. There were 262 cases in which the mothers were certain that they had contracted rubella during the particular pregnancy under consideration. A hundred and twenty-nine of these infants living in the Brisbane area were examined and 37 found to have a serious congenital defect, while in the country group, comprising 128 cases, 36 mothers stated that their children had congenital abnormalities. It is interesting that the percentage of children affected is 28.7 in the Brisbane area and 28.2 for the country districts. In a a similar study, in which questionnaires were sent to 6,000 physicians in Massachusetts, 49 women were reported as having rubella during pregnancy (50). Six infants from these gestations presented serious congenital malformations, representing 12.3 per cent. If in the Massachusetts study only those cases of rubella which occurred in the first trimester are considered, 22.7 per cent of the infants were found to be congenitally defective.

There have been several reports of congenital malformations following maternal infection with mumps and chicken pox. From Milwaukee comes a study of 533 women who had either rubella, mumps or chicken pox from 1942 to 1945 (51). In this group, there were 665 children born either before the onset of the disease or after it was over. Nine-tenths of 1 per cent of these infants had congenital malformations There were 33 children born of pregnancies in which the mothers had one of the three virus diseases. There was only one congenital abnormality, that of a unilateral hare-lip child, in a mother who had measles in the fourth month of her pregnancy. This series is too small for statistical evaluation, but it is only by investigations of this kind that adequate data can be gathered regarding the effect of these virus diseases.

In an attempt to evaluate rubella in pregnancy as an etiological factor in stillbirth, Swan (52) sent questionnaires to 1,265 mothers who had stillborn

also had varicella: mumps, two cases; rubella, one case, mumps and whoop-

nancy. In these 16 cases, there were eight in which there was no known cause for stillbirths.

# DISEASES OF THE NERVOUS SYSTEM

## NEUROLOGY

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### INTRODUCTION

Neurological literature has swung into its stride again following the halting pace of wartime. While new textbooks of neurology have not appeared, a number of standard texts have been revised for new editions (10, 25). Bucy (82) has largely rewritten Grinker's *Neurology*, making it more useful to the student. Walshe (203) has published in book form a series of six papers, originally appearing in journals, which are critical discussions of the basic principles of neurology.

A new textbook of neuroanatomy by Brodal (21) relating structure to function has appeared, as well as new editions of two of the standard neuroanatomy textbooks (131, 193). Neuropathology is well represented in the literature, a textbook by Lichtenstein (120) and an atlas by Blackwood, Dodds & Sommerville (18) appearing this year, as well as a very extensively illustrated atlas of peripheral nerve injuries by Lyons & Woodhall (124). Neuroradiology is well covered in a monograph by Orley (142). Neurological nursing has received attention, an excellent text being written by de Gutierrez-Mahoney & Carini (48) and a smaller monograph by Klemme (111).

The current literature has been so voluminous that more than 700 neurological articles have been consulted for this review. No attempt is made to cover the entire field of neurology in this discussion Many interesting subjects such as clinical physiology of the brainstem, diencephalon and cerebral cortex have been omitted because of lack of space. Disorders of the sympathetic nervous system are covered in other sections of this book. Psychosurgery, recently well outlined by Solomon (189), is not discussed since it pertains largely to psychiatry. Neurological disorders associated with systemic disease, not included in this review, will be found in other chapters. Within the limited field selected it has been possible to refer to only a few representative papers on each topic. Equally good presentations might be quoted from not only the United States, but South American or European journals This review covers the available neurological literature from 1 July, 1948 to 31 August, 1949.

### SPECIAL DIAGNOSTIC TECHNIQUES

*Angiography.*—Cerebral angiography is a simple and useful technical aid in the diagnosis of cerebral tumors, abscesses, and vascular anomalies. Percutaneous puncture of the carotid artery, performed by a skillful operator, may be accomplished rapidly and accurately in 95 per cent of cases (157)

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(204) and Gastaut (75) have demonstrated the value of intermittent photic stimulation in the electroencephalographic examination. They are able to induce epileptic manifestations in a high percentage of cases by this means with or without the addition of a small amount of metrazol given intravenously.

*Electromyography.*—The electrical phenomena associated with muscular activity have proved valuable aids in the diagnosis of disorders of the peripheral nervous system. Denny-Brown (49), Buchthal (24), and Petersen & Kugelberg (151) discuss the normal electromyogram In pure myopathies, maximal muscle contraction is generally accompanied by interfering electrical activity of many asynchronously firing units with reduced amplitude. Electromyography is useful in following the course of peripheral nerve lesions, poliomyelitis (94a), and may aid in the localization of tumors of the spinal cord (95).

*Radioactive isotopes.*—When radioactive tracers became available, it was natural that attempts should be made to utilize them for localization of brain tumors (134). After demonstrating that fluorescein was concentrated within cerebral neoplasms, Moore *et al.* (135) added radioactive iodine to produce diiodofluorescein. The location of the gamma radiation of this compound was then determined by counters applied to the head. Analysis of the amount of radiation enabled a correct localizing diagnosis to be made in most of the cases.

Another radioactive isotope, $P^{32}$, has been used for localization of brain tumors (58, 182, 183). Because the radiation has low penetration, this isotope, concentrated in the tumor, can only be detected when the counter is within 5 to 6 mm. of the neoplastic tissue. This has the advantage of insuring more accurate localization than can be made with radioactive diiodofluorescein, but only after the skull has been opened

## Peripheral Nerves

The follow-up of the peripheral nerve injuries of World War II should provide valuable information concerning the handling of such wounds (215). At present the treatment follows the techniques developed during the war (34).

*Nerve grafting.*—Autogenous nerve grafting has proven to be valuable and, in the hands of Seddon (181), almost as reliable as an end-to-end suture Both single and cable grafts were satisfactory, but the proximal was usually better than the peripheral stump for a graft. Somewhat similar results are reported by Bjorksten (2) Heterografts were complete failures, but cable and full thickness autogenous grafts were successful in varying degrees in more than 50 per cent of the cases.

*Neuropathy*—Neuropathy may be induced by many factors. The etiology of the so-called infectious polyneuritis remains obscure, but the disease is recognized to involve much more of the nervous system than the peripheral nerves. Wilcox (211), Scheinker (172), and Haymaker & Kernohan (92)

Even vertebral puncture is not too difficult a technique (194). Diodrast in 35 per cent or 50 per cent solution has caused few reactions other than the unpleasantness experienced at the time of injection. In 2 per cent of cases vascular spasm, probably due to the direct effect of the drug on the vascular musculature, has occasioned a temporary hemiparesis, with or without an aphasia. The use of the more dilute solutions has practically abolished the convulsive complications experienced with the 70 per cent solution. If diodrast is injected outside the vessel, it is rapidly absorbed and excreted. Such is not the case with thorotrast, for it may remain in the neck for years causing a chronic inflammatory mass. Amory & Bunch (6) report seven cases of this unhappy sequela, and in a clinic on this subject at George Washington University (76) some six other cases were collected. It would seem inadvisable to use this radioactive substance, although it may give slightly more detailed angiograms.

A number of different types of x-ray equipment have been proposed for making rapid and numerous films during the passage of the contrast medium through the intracranial circulation (41, 64, 160, 212). Probably the ideal solution is cinematography. It is obvious now that one or two random films taken at variable or fixed intervals during the cerebral circulation of the diodrast will not suffice for an adequate examination.

*Pneumoencephalography.*—The after-effects of pneumoencephalography may be much lessened by the routine administration of 95 per cent oxygen in a tent at the rate of eight liters per minute (112). The cervical subarachnoid space may be well visualized by lumbar insufflation of air. Marks & Livingston (127) have demonstrated syringomyelic distention of the spinal cord and the Arnold-Chiari malformation by this technique

*Electroencephalography.*—Electroencephalography is a well-recognized aid in the diagnosis of epilepsy and brain tumors (39, 40, 101). It may give valuable information in other nervous disorders such as behavior disorders and cerebral vascular disease (118, 132). Changes may be demonstrated in the electroencephalogram of patients receiving shock therapy. These alterations are more pronounced in the patients who had abnormal preshock records; Kennard & Willner (107) suggest that preliminary electroencephalograms may be of diagnostic and prognostic importance.

The value of the electroencephalograms has been enhanced by the introduction of additional leads from the base of the skull (8, 60, 126) and various activating techniques (105a). The use of pharyngeal and tympanic leads has made it easier to localize disturbances arising from the poles and medial surface of the temporal lobes Recording during natural or induced sleep may bring out alterations or accentuate asymmetries in the cerebral activity Cress & Gibbs (37) believe that such asymmetries, resulting from vascular or traumatic encephalopathies, are more accessible during sleep. Other activating techniques have been discussed by Kaufman & Watson (105a). Metrazol, injected intravenously, rapidly or slowly, has proved of value in activating epileptic foci in 60 to 90 per cent of cases (105). Walter & Walter

TABLE I

RESULTS OF OPERATION FOR PROLAPSED INTERVERTEBRAL DISC

| Author | Number of cases | Percentage Results | | |
|---|---|---|---|---|
| | | Good | Fair | Poor |
| Crawford *et al.* (36) | 346 | 61 | 12 | 27 |
| Echols (57) | 101 | 46.5 | 44.5 | 8.9 |
| Grant *et al.* (79) | 95 | 60 | | 7 |
| Gurdjian & Webster (83) | 80 | 68 | 20 | 12 |
| Raaf & Berglund (159) | 160 | 61.25 | 28.75 | 10 |
| Spurling & Grantham (190) | 327 | 40 | 39.2 | 20.8 |

*Traumatic myelopathy.*—Kuhn & Macht (114) state that following transverse injuries of the spinal cord in man, reflex activity passes through five stages: (*a*) spinal shock; (*b*) minimal reflex activity, (*c*) flexor spasm; (*d*) alternating flexor and extensor spasm, and (*e*) extensor spasm In the stage of flexor spasm the muscular contractions may be so frequent and powerful that the patient becomes emaciated and develops bed sores. The spasms may be relieved by anterior root section (68), or by the intrathecal injection of alcohol, as advocated by Shelden & Bors (184) and practiced by Cooper & Hoen (33) Bladder function is usually favorably modified by this procedure although sexual function, which is surprisingly well preserved in many paraplegics according to Munro *et al.* (137), may be markedly decreased or abolished.

### INFECTIONS OF THE NERVOUS SYSTEM

The accurate and early diagnosis of infections of the nervous system has become of increasing importance as antibiotic agents have been developed (216). If therapy is delayed, the inflammatory process may irreparably damage the brain or the reparative processes may produce severe neurological sequelae even though the infection is eliminated. A third consideration has arisen with the too enthusiastic use of intrathecal medication. This concerns the toxic reactions of the meninges, spinal cord, and brain to the antibiotic agent, as Wilson *et al.* emphasize (213). It has been repeatedly demonstrated that intrathecal administration of large amounts of any of the present antibiotic agents may cause irreparable damage to the nervous system. For this reason, in many infections the tendency has been to give massive doses of the antibiotic agent systemically and little, if any, intrathecally (51).

*Subdural empyema.*—Infection of the subdural space requires the local instillation of the appropriate antibiotic agent, Keith (106) emphasizes, since systemically administered penicillin does not reach the subdural space. Schiller *et al.* (173) advise early drainage and irrigation of the subdural

emphasize that the process may implicate the central nervous system at any level. Nor is the disease always benign, as may be judged by Haymaker & Kernohan's (92) review of 50 fatal cases. Wilcox (211) reports a 37 per cent mortality. Furmanski (73) states that the pathological process involving the peripheral nerve is reversible until the axone has been severely damaged. He found British Anti-Lewisite (BAL) therapy effective in a number of cases of severe peripheral neuropathies.

*Amputation stumps.*—Painful amputation stumps and phantom limb fortunately have not been a frequent occurrence as the result of injuries of World War II in the United States of America. This is probably due to the prompt and excellent surgical care, the psychological counseling and the physical and social rehabilitation given amputees. Russell (167) reports that hammering the neuroma to produce a concussion of the nerve endings gave relief in seven cases. He advises his patients to pound "the devil out of the stump" when it is painful. Browder & Gallagher (22) sectioned the posterior column for painful phantom limb Good results were obtained with phantom lower limbs but they were less satisfactory when the upper extremity was involved.

## Spinal Cord and its Roots

*Intervertebral disc syndrome.*—Mixter (133), who first fully recognized the role of herniated intervertebral discs in "sciatica," has given a short history of the evolution of the syndrome. Although a prolapsed disc is the usual cause of sciatic pain, other factors may be responsible. Hadley (84) emphasizes the role of constriction of the intervertebral foramen. Occasionally intraspinal tumors, such as the aneurysm reported by Scoville (178), will cause "sciatica." On the other hand a protruded disc may simulate a tumor of the spinal cord (108) or, in the cervical region, degenerative spinal cord disease as reported by Bucy *et al.* (26).

Usually the diagnosis of prolapsed disc can be made on clinical signs and symptoms. Regular roentgenograms of the spine are of little value except to eliminate spinal pathology as a cause of the symptoms A narrowed interspace is not an indication of a prolapsed disc, according to Grant *et al.* (79) and Gurdjian & Webster (83). In doubtful cases myelography is necessary, but may be misleading in 25 to 30 per cent of cases Murphy (138) reported two cases in which myelography disclosed major disc protrusions on the side opposite the clinical symptoms

The results of the operative treatment for prolapsed disc are uniformly good (TABLE I) Grant *et al* (79) thought that the results were better in those cases in which the disc was found to be frankly ruptured through the annulus fibrosis Spinal fusion does not seem to modify the results according to Echols (57) and Crawford *et al* (36) Nor did the operative technique—laminectomy, hemilaminectomy or interlaminar removal—seem to play a significant role. The poor results may be the result of intraneural changes which Lindblom & Rexed (121) describe as the result of disc protrusion.

diagnosis of tuberculous meningitis, especially in countries in which this disease is not prevalent. Where the incidence of tuberculosis is high, every patient, particularly children who have slight malaise, irritability, and anorexia, should be suspected of tuberculous meningitis. At this time, although the physical and neurological examinations may be normal, Rubie & Mohun (165) state that the spinal fluid may have a slight lymphocytosis, increased protein, and decreased sugar content. In most instances at this stage the tubercle bacillus cannot be found on direct smear and the diagnosis can only be confirmed by culture of the spinal fluid. If treatment is not started until the neurological signs, such as cranial nerve involvement, stiff neck, headaches, and vomiting have developed, the treatment is much less effective.

It would seem that the sensitivity of the organism to streptomycin varies from case to case, as well as the resistance of the patient. In some patients tuberculous meningitis has developed during the treatment of miliary tuberculosis with streptomycin. This, perhaps, is not unexpected since streptomycin enters the spinal fluid in extremely minimal amounts.

In general the treatment of tuberculous meningitis has been by systemic administration of streptomycin, approximately 2 gm. daily, plus the intrathecal injection of streptomycin in doses varying from 100 to 500 mg. daily. It would seem to be quite important to continue the treatment of a patient with tuberculous meningitis for a rather long period of time, at least four and perhaps six months. With dihydrostreptomycin the incidence of auditory involvement is much less.

Bunn (27) states that 37 per cent of the patients in his series treated for tuberculous meningitis are living. This is approximately the same as other authors report [Choremis *et al.* (31), 42 per cent of 50 cases].

*Brain abscess.*—With the use of antibiotic agents the symptomatology of brain abscesses has radically changed. The signs of systemic toxicity are observed rarely, and the abscess manifests itself by evidence of an expanding intracranial lesion. Arteriography may indicate not only the presence of a mass, but its nature (59), thus making its treatment simple. Tapping the abscess through a burr hole, evacuation of the pus, and injection of thorotrast is worth a trial, for practically half of the abscesses may be eliminated by two or three taps. If the pyograms (199) show that the abscess is increasing in size it may be removed *in toto* as a brain tumor. An appropriate antibiotic should be left in the bed of the abscess This form of therapy is highly successful, although complications such as meningitis or inflammatory occlusions of the ventricular system occasionally result (38). Metastatic brain abscesses, usually from the lung, state Rizzoli *et al.* (162) and Pennybacker & Sellors (149), should be handled in the same way and later the primary condition treated. Other rarer types of abscess, tubercular (140), actinomycotic (175), suppurated hydatid cyst (140), *Clostridium welchii* (32), may be excised with success.

*Encephalomyelitis.*—Allergic encephalomyelitis may be produced by intraperitoneal injection of brain tissue and adjuvants in more than 50 per

empyema with solutions of penicillin or streptomycin for best results. This advice is equally applicable to spinal, extradural (94) or subdural infections, for Freedman & Alpers (67) found that the myelopathy was due to impairment of the circulation of the spinal cord.

*Purulent meningitides.*—The treatment of the common purulent meningitides—meningococcic, pneumococcic, staphylococcic, and streptococcic —has been fairly well standardized. Dowling *et al.* (52) report excellent results in meningococcic meningitis by the use of sulfadiazine or sulfamerizine. If it is necessary to employ penicillin due to lack of response or a fulminating infection, this antibiotic agent is given in a dose of 1 million units intramuscularly every 2 hr. Pneumococcic meningitis, according to Waring & Weinstein (205), is usually treated by systemic administration of penicillin in doses of 500 to 2 million units daily along with 10 to 20 thousand units of penicillin intrathecally. Sulfonamide drugs, particularly sulfadiazine, are usually advocated for systemic administration. However, Dowling *et al.* (51) and Lowry & Quilligan (122) have demonstrated that this type of meningitis may be treated just as successfully with large doses of penicillin without any intrathecal therapy, approximately 1 million units of penicillin being given systemically every 2 hr. Staphylococcic and streptococcic meningitis are usually treated by systemic and intrathecal penicillin. Again Dowling *et al.* (51) maintain that with massive doses of penicillin this disease may be successfully treated without the use of intrathecal therapy. If signs of recovery are not present shortly after the beginning of medical management, Cairns (28) believes that surgical procedures should be considered in order to obtain a more adequate distribution of the antibiotic agents. He states that the ventricular fluid may be blocked by fibrin deposits in the basal cisterns. Accordingly he advocates the introduction of a catheter into the ventricle, basal cistern, or subdural space as indicated for the direct introduction of the antibiotic material

La Londe & Gardner (115) call attention to urea as an adjunct to sulfonamide treatment in certain resistant cases of bacterial meningitis. The use of this drug has proved of value when other chemotherapeutic and antibiotic agents have failed.

The primary source of infection should be adequately treated, surgically if necessary, Kershman & Petersen state (110). Mount (136) emphasizes that congenital dermal sinus should be considered as a source of meningeal, spinal, or cerebral infection. Such sinuses may communicate with and infect intraspinal dermoids (169).

*Tuberculous meningitis*—The results of treatment of tuberculous meningitis with streptomycin, with or without other drugs (125), seem to depend upon several factors Perhaps the most important factor is the stage of the disease in which the treatment is started Choremis *et al.* (31) and practically all authors have emphasized that the results are much superior if streptomycin therapy is started within a week or two of the onset of symptoms. As Craig (35) states, it is, of course, extremely difficult to make an early

not yet certain whether the virus enters through the respiratory or alimentary tract in man. Many cases appear to be unaccompanied by paralysis. Paul (145) states that in a series of cases in 1916, 1935, and 1947 the incidence of nonparalytic poliomyelitis was 13, 33, and 70 per cent respectively. It would seem that severe physical activity in the preparalytic stage is likely to be associated with a grave prognosis (87, 166). Pollock *et al.* (154) have demonstrated that there is no evidence of muscle spasm in the early stage of poliomyelitis, such as has been claimed. Osborne *et al.* (143) believe that early and late electrical stimulation of involved muscles is desirable for two reasons: (*a*) it increases the bulk of atrophied muscles and lessens the atrophy in early paralysis, and (*b*) it improves the strength of the muscle.

Brown & Baker (23) believe that bulbar poliomeylitis may be divided into four syndromes depending upon the locus of the major process. (*a*) cranial nerve; (*b*) respiratory, (*c*) circulatory, and (*d*) encephalitic. Supportive therapy is the main guide for this type of poliomyelitis. Stimson (192) outlines the treatment as (*a*) reassurance, (*b*) postural drainage, (*c*) 10 per cent glucose intravenously, (*d*) oxygen, and (*e*) minimum handling. There appears to be agreement on the advisability of early tracheotomy in most of these cases (11, 208).

## Vascular Disturbances

The correlation between retinal arteriosclerosis and cerebral arteriosclerosis is not generally reliable, according to Alpers *et al.* (4). While the presence of retinal arteriosclerosis indicates the possibility of cerebral arteriosclerosis of the basal arteries, it gives no indication of the state of the vessels of the cerebral cortex, meninges, or basal ganglia. Nor is the absence of retinal arteriosclerosis a proof of the absence of cerebral arteriosclerosis. Shenkin *et al.* (185, 186) concluded that the blood entering one internal carotid artery was distributed almost entirely to the ipsilateral cerebral hemisphere and drained by the corresponding internal jugular vein. When intracranial hypertension was reduced by ventricular puncture the cerebral blood flow was not altered greatly, whereas it increased when the pressure was reduced by means of intravenous glucose solution.

Young & Karnosh (217), using an injection technique, failed to find any evidence of precapillary anastomosis within the substance of the internal capsule, which is irrigated essentially by the terminal branches of the arterioles of the anterior perforated system This may explain the frequency of capsular hemiplegias

Cerebral hemorrhage usually does not cause immediate sudden death. Rose (164) found that the shortest survival period of a patient with cerebral hemorrhage dying within a hospital was two hours Of 205 cases 80 per cent were dead in 24 hr Brainstem hemorrhages apparently cause death early, and strangely enough, cerebellar hemorrhages are compatible with a long survival period Surgical removal of the clot, even in the brainstem, may be successfully accomplished (180).

cent of guinea pigs (30, 61, 103, 123). The adjuvants alone are ineffective in producing the condition which cannot be transferred to other guinea pigs. The disease usually appears about the 32nd day after inoculation. The lesions, predominantly in the white matter, are disseminated, perivenous, and characterized by curious, diffuse proliferation of adventitious cells, softening, and a zone of microglia proliferation. Ferraro & Cazzullo (62, 63) found that the injection of a brain emulsion prior to the inoculation of the disease-producing emulsion protects the animals from the development of the encephalomyelitis.

The virus diseases of the central nervous system were the subject of a symposium at the Fourth International Neurological Congress. The virus of herpes zoster may attack the nervous system, producing a variety of encephalitic syndromes (91). Western equine encephalomyelitis has been successfully treated by Saphir & Milzer (170) with gamma globulin. The diagnosis may be difficult, for the spinal fluid may be normal. It is made by the demonstration of significant rise in titer of both complement fixing and neutralizing antibodies for the virus. The sequelae of the eastern equine encephalomyelitis have been quite serious. Ayres & Feemester (9) report six out of nine survivors having permanent sequelae such as hemiplegia, mental deficiency, epilepsy, etc. Only one survivor was completely well. That choriomeningitis may be transmitted by mice was shown by Havens (90). His patient was a worker in a granary harboring mice, the brains of which contained the virus. Encephalopathies following a number of systemic diseases have been reported (93).

A number of rare encephalitides have been discussed in the past year. Mengo encephalomyelitis was reported by Dick and his co-workers (50). Cerebral complications may follow tetanus antitoxin (65). The rheumatic encephalitides may produce a number of neurological syndromes, including chorea and torsion dystonia (17). Cysticercosis cerebri is a relatively common disease in some European and South American countries. Stepien & Chorobski (191) classify their cases in three groups: (*a*) those cases with focal signs of an intracranial tumor; (*b*) those cases with cerebral edema and psychic disturbances, and (*c*) those cases with internal hydrocephalus due to a basal cysticercosis. Without the history of infection or the roentgenological demonstration of parasites in muscle the diagnosis cannot be made. The treatment of choice is surgical and is followed by good results in about 50 per cent of cases. Even if all the parasites are not removed, a partial excision with decompression may result in improvement. A short circuiting operation may be performed for the cases of internal hydrocephalus due to basal involvement. Davidson *et al.* (46) report two cases of louping-ill virus meningo-encephalomyelitis in man with complete recovery. Cases of cerebral schistosomiasis (13) and toxoplasmosis (72, 98) are also presented.

*Poliomyelitis.*—Bodian (20) reviews his work on experimental poliomyelitis in a comprehensive article. Although the mode of extension in experimental animals has been extensively studied, Sabin (168) reports that it is

not yet certain whether the virus enters through the respiratory or alimentary tract in man. Many cases appear to be unaccompanied by paralysis. Paul (145) states that in a series of cases in 1916, 1935, and 1947 the incidence of nonparalytic poliomyelitis was 13, 33, and 70 per cent respectively. It would seem that severe physical activity in the preparalytic stage is likely to be associated with a grave prognosis (87, 166). Pollock *et al.* (154) have demonstrated that there is no evidence of muscle spasm in the early stage of poliomyelitis, such as has been claimed. Osborne *et al.* (143) believe that early and late electrical stimulation of involved muscles is desirable for two reasons (*a*) it increases the bulk of atrophied muscles and lessens the atrophy in early paralysis, and (*b*) it improves the strength of the muscle.

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As the result of angiography, interest has revived in intracranial aneurysms and angiomas. Robertson (163) discusses the clinical findings resulting from aneurysms in different parts of the cerebral vascular tree. Intracerebral hemorrhage is a common occurrence due to rupture of an aneurysm and has a somewhat poorer prognosis than a subarachnoid leak. Because of this fact Jefferson (102) believes that ventriculography should be carried out to localize the clot which may have ruptured into a ventricle. This is particularly pertinent in a patient who remains unconscious or mentally confused. Arteriography may be performed safely within a few hours of a cerebral vascular accident according to Wechsler & Gross (206). Although many aneurysms are visualized by this technique, the failure to demonstrate an aneurysm does not eliminate the possibility (5). If the lesion can be demonstrated the aneurysm may be clipped or trapped (99, 176, 194). Such procedures are not without risk. Matson & Woodhall (129) report a case of intracranial and cervical trap ligation of the carotid artery complicated by blindness of the homolateral eye.

Recently Sciaroni (177) and Beck *et al* (16) have attempted to reverse the cerebral circulation to increase the blood supply in patients with mental retardation, paralysis, or convulsions by establishing a cervical (carotid-jugular) arteriovenous fistula. The work has not been followed sufficiently long to judge the merits of the procedure

## Brain Tumors

*Pathology*—The classification of brain tumors still is being discussed (218). In an attempt to make the classification of brain tumors correspond to that of other tumors, Svien *et al* (195) have proposed one based upon the concept of anaplasia. They divide the gliomas into four classes: astrocytoma, ependymoma, oligodendroglioma, and neuro-astrocytoma, each one being graded 1 to 4 depending upon the evidence of malignancy as seen histologically. A fifth class, medulloblastoma, are not so graded. This classification, the authors argue, is not only simpler than that of Bailey and Cushing, but more serviceable to the surgeon, who is concerned more with the degree of malignancy of a neoplasm than with its specific histological appearance.

*Tumors of the cerebral hemispheres*—The clinical characteristics and biology of glioblastoma, the malignant gliomas of adult life, are discussed by Davis *et al.* (45) on the basis of a series of 211 verified cases. The authors divide their tumors into angiothrombotic and angioproliferative groups. The survival time was longer in the latter group. It was definitely longer in the patients having radical removal of the tumor than in those having only a surgical biopsy. Removal of the bone flap seemed also to decrease the postoperative mortality. Roentgen ray therapy may prolong the life expectancy. However, in seven tumors there was a transition from a rather benign to a more malignant glioblastoma during the treatment Brain necrosis may result from radiation therapy, Pennybacker & Russell (148) maintain. Vascular tumors of the brain may be successfully removed or coagulated with the electrosurgical unit, according to Trupp & Sachs (198).

*Posterior fossa tumors.*—The medulloblastomas are discussed by Pierce *et al.* (153) who suggest that only an aspirated biopsy is necessary before giving x-ray therapy. This technique seems to be somewhat unreliable, for from the illustrations of the authors it is not easy to differentiate the normal cerebellar cortex from the neoplastic tissue. The difficulty in diagnosis of tumors in the cerebellopontine angle is emphasized by Alpers & Forster (3). Revilla (161) gives a differential diagnosis of such tumors on the basis of Dandy's cases. Kernohan *et al.* (109) believe that it is very difficult to make the diagnosis of glioma of the cerebellopontine angle preoperatively. Olivecrona & Givre (141) present the statistics of 250 cases of acoustic neurinoma operated upon by the senior author. There was a mortality of 23.6 per cent. The authors believe that complete extirpation of the tumor is much more satisfactory than partial or intracapsular removal. In approximately one half of the cases Olivecrona is able to save the facial nerve. It is remarkable that approximately 80 per cent of the cases surviving the operation are now working.

*Tumors of the ventricular system.*—Greenwood (81) reports eight cases of paraphysial cysts of the third ventricle which are particularly amenable to surgical treatment. The gliomas of the septum pellucidum may occasionally be successfully extirpated, as in one case reported by French & Bucy (71). Intraventricular epidermoids (53) give a characteristic appearance in pneumoencephalograms. Hauser & Elkins (89) describe an irregular streaking due to gas about the folds of the tumor in the ventricle. Torkildsen (197) believes that tumors in or near the third ventricle, if not obviously removable, are best treated by a short circuiting operation. Tolosa (196) discusses the various types of ventriculostomies. Horrax (96) favors such a procedure for pineal tumors which are difficult to remove surgically. Of 12 patients treated by decompression and x-ray therapy seven are alive 2 to 14 years after operation, whereas only three patients are surviving of 10 who had a grossly complete extirpation of a pineal tumor. Tumors about the pituitary region can usually be diagnosed by regular roentgenograms of the skull (86), but suprasellar neoplasms require pneumoencephalography for their demonstration (174).

Greenwood (80) states that 75 per cent of patients with benign brain tumors are able to return to a useful existence. An early diagnosis makes not only the surgical removal easier, but the end results better.

## Head Injuries

Barker (12), studying injuries to the superior longitudinal sinus, found that spasticity and weakness of the legs occurred early and without a period of flaccidity In children the general disturbances of cerebral function—confusion, coma, and vomiting—often follow a head injury. Woodhall (214) discusses the treatment of cerebral trauma. Extradural hematomas in children are not uncommon, but the symptomatology differs from that in adults Ingraham *et al.* (97) found that only three of their 20 patients had an initial loss of consciousness; seven later became unconscious. Swelling

at the site of the injury was common and anemia may result from the loss of blood into the tissues and hematoma. Extradural hematomas, if in unusual sites (7), may be difficult to locate. Ventriculography may be necessary (128). Raaf (158) discusses his experience with massive extradural hematomas, emphasizing the need for early diagnosis and prompt surgical intervention. Subdural hematomas may be chronic, subacute, or acute. Echlin (56) states that the symptomatology is often vague and the diagnosis must be made on a high incidence of suspicion rather than definite neurological findings Following the evacuation of chronic subdural hematomas the compressed brain may not expand. La Londe & Gardner (116) advocate the relief of this hypotension by the spinal injection of physiological saline. Traumatic cerebrospinal otorrhea or rhinorrhea, if treated by prophylactic administration of penicillin and sulfadiazine, usually clears up spontaneously. A persistent rhinorrhea has been repaired by Adson & Uihlein (1) through a bifrontal craniotomy by plugging the bony defect with wax and covering it with membrane. The dural rent is closed with a double layer of sutures enclosing a strip of muscle.

*Cranioplasty.*—The repair of cranial defects has been made with tantalum plates in recent years. Bates *et al.* (14, 15) state that zirconium is a very satisfactory agent for cranioplasty Weiford & Gardner (207) believe that cranial defects should be repaired early, even in the presence of infection which is being adequately treated by antibiotic therapy Lewin *et al.* (119) found, on follow-up, that 94 of 128 cranioplasties were satisfactory Eleven plates had to be removed; for infection, 5, intracerebral complications, 4, or cosmetic defects, 2. White (209) in a survey of cranioplasties made in World War II, reports 151 patients with some complication and 114 requiring removal of the plate, in most cases for infection.

## Epilepsy

Penfield (146) believes that the classification of the epilepsies should serve as a guide to therapy and prognosis. Accordingly he suggests that seizures be grouped as (*a*) cerebral seizures, (*b*) focal cerebral seizures, and (*c*) idiopathic epilepsy. When possible the classification should include also the localization, pattern, and cause of the fit. That birth trauma may be a factor in idiopathic epilepsy is suggested by Nielsen & Butler's (139) finding that convulsions were nearly twice as common in the first-born as in sub-

examined by the electroencephalogram Jasper (100) states that the local random spike discharge characterizes a focal epileptogenic lesion; generalized electroencephalographic abnormalities are present in idiopathic epilepsy.

*Focal epilepsy.*—The epilepsies following cerebral trauma, according to Walker (201), may be clinically generalized or focal, but the initial discharge,

as determined electroencephalographically, is focal. Walker (201) & White *et al.* (210) conclude that surgical treatment for epilepsy secondary to cerebral trauma and infection will relieve the epilepsy in approximately 50 per cent of cases. Even infants may be operated upon with good results (147). An interesting case of focal, sensory precipitated epilepsy, presented by Forster *et al.* (66), was relieved of attacks by cortical resection of the focus.

*Psychomotor epilepsy.*—Psychomotor epilepsy is characterized by confusion and automatic repetitive movements, usually accompanied by manifestations of fear, anger or rage Gibbs *et al.* (77) state that this type of epilepsy is associated with unilateral or bilateral anterior temporal spiking which may be demonstrated particularly well during natural or induced sleep (74).

*Medical therapy.*—Merritt (130) believes that dilantin and phenobarbital are the most effective drugs in the treatment of epilepsy Peterman (150) thinks that the ketogenic diet is the most reliable therapy, but emphasizes that treatment must be considered for each case. Tridione is particularly effective in petit mal epilepsy (44) Mesantoin is a useful anticonvulsant drug (42), but aplastic anemia may occur, as reported by Bloom *et al* (19) Phenurone is said by Gibbs *et al* (78) to possess superior anticonvulsant properties Alone or in combination with mesantoin it will control some patients not helped by other drugs In many patients it has an unpleasant side effect on the personality. For status epilepticus delvinal sodium vinobarbital is recommended by Davidoff *et al.* (43) and paraldehyde by De Elio *et al.* (47).

*Surgical therapy.*—In those cases of focal epilepsy not relieved by medical therapy, it is usually possible to locate the epileptogenic focus by direct recording from the exposed brain. Walker (201) describes the surgical techniques in a small monograph

## MISCELLANEOUS

*Ménière's syndrome*—Paroxysmal vertigo of aural origin is described by Walker (202) who believes that surgical section of the vestibular portion of the eighth nerve is advisable if medical therapy—histamine, nicotinic acid, etc—is not successful Passe & Seymour (144) have divided the vertebral artery and removed the stellate ganglion on the side of the affected ear in 12 patients with good results in all but one case

*Myasthenia gravis*—The role of the thymus in myasthenia gravis continues to be a subject of investigation Castleman & Norris (29) found that 10 of 35 cases of myasthenia studied had thymic neoplasm. The non-neoplastic thymus gland exhibited varying degrees of involution Harvey (88) reports seven thymic tumors in 35 cases explored Eaton *et al.* (55) found 15 thymomas in 32 thymectomies. Following removal of the thymus, approximately 25 per cent of the patients were markedly improved (TABLE II). There was a higher incidence of remissions in the patients with thymic tumors.

TABLE II

Results of Thymectomy

| Author | Number of Cases | Much Improved | Slightly Improved | Unchanged | Deaths |
|---|---|---|---|---|---|
| Harvey (88) | 32 | 8 | 12 | 9 | 3 |
| Eaton *et al.* (55) | 32 | 10 | 9 | 9 | 4 |

*Pain*.—The surgical treatment of pain has emphasized the relief of suffering. Although interruption of pain tracts (104), as reviewed by Sjoqvist (188), is satisfactory, not infrequently the patient's reaction to his illness nullifies the beneficial result of the operation. For that reason prefrontal lobotomy, as performed by Poppen (156), or one of its variations, topectomy (155),

the operation, if asked, they usually state they still have severe discomfort (54, 70, 85, 113). Their reaction to their suffering has been changed, but too often their reaction to their environment is also changed unfavorably. This side effect, Le Beau says (117), is less pronounced after topectomy. It is rarely seen as the result of unilateral lobotomy, which in some patients is adequate to relieve pain (171, 200).

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# PSYCHIATRY[1]

By John C Whitehorn
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The recent contributions in the field of psychiatry do not fit together into any clearly discernible strategic advance but appear as sporadic thrusts at widely scattered points.

*Malononitrile.*—Great hopes have been raised by the work of Caspersson and his associates for a very fundamental increase in the knowledge of the physiological substratum of mental functioning Methods for the microspectrographic examination of cells in the nervous system, obtainable by biopsy, have enabled these Swedish investigators to gain much information about nucleoprotein production therein. Malononitrile has been found to stimulate such production. Hydén & Hartelius (1) have published a monograph (in English) presenting their investigations in the rabbit and in man, including a trial of the possible therapeutic value of malononitrile in 30 patients afflicted with various psychopathological conditions. This is an important publication which is undoubtedly being eagerly studied by psychiatrists and neurophysiologists in all countries In a brief review with bibliographic references they present the basic work of Caspersson. Caspersson has also presented his work to an American audience in the Salmon Lectures in New York, in November, 1948 Hydén & Hartelius report that small doses of malononitrile (3 to 4 mg. per kg. body weight) increase the amount of nucleic acid of the ribose type in the nerve cells from 1.7 per cent to 3.1 per cent. Evidence was adduced that motor and sensory functions are related to these chemical changes. The authors' clinical experimentation on psychiatric patients was designed to test the effect of malononitrile on psychic functions. They state:

> In cases of endogenous depression, malononitrile causes an initial accentuation of psychomotor retardation and depression, followed by psychomotor spontaneity and euphoria. In schizophrenia, malononitrile causes an initial accentuation of autism and katatonia, followed by increased contact and mental release.

Some of the material reported by Hydén & Hartelius is concerned with biopsy material obtained in connection with frontal lobotomy. This is just one instance of the widespread interest in lobotomy and the scientific utilization of the opportunities opened by lobotomy.

*Frontal lobotomy.*—A very recent paper by Kolb (2) provides an extensive review of publications in this field during the period of something more than a decade since Moniz introduced pre-frontal lobotomy for the treatment of certain psychoses In Kolb's review he attempts also an evaluation of re-

[1] This review covers the period from approximately November, 1947 to August, 1949

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economic differences By its award of the Hofheimer prize, the American Psychiatric Association has given special emphasis to a study by Pasamanick (8) of the personality development of a group of negro infants, who by reason of war-time conditions had approximately the same nutritional conditions as the control white children. Their physical and mental growth, as gauged by Gesell's criteria, were not appreciably different from the controls.

*Group psychotherapy.*—In matters of psychodynamic significance, special interest has recently been shown in group dynamics, especially group psychotherapy. Foulkes (9) has published a small monograph presenting his experience and understanding of group psychotherapy. A good general discussion and orientation concerning the aims, methods, and results of group psychotherapy has been offered by Burchard, Michaels & Kotkov (10). Preliminary reports by Powdermaker & Frank (11) concerning those investigations of group psychotherapy supported by the Veterans Administration have indicated the probable value of intensive study of the process of psychotherapy in groups for the understanding of psychotherapy in general. Their work is notable for the critical use of observers, a valuable investigative aid not practicable in the study of individual psychotherapy.

*Social dynamics*—The understanding and control of social dynamics has been the theme of a provocative paper by Chisholm (12) on "The Future of Psychiatry," in which he says

[illegible] intra- and inter-human relations are studied, in the interests of prevention of personal and social maladjustment, and in the hope of racial survival.

*International Congress on Mental Health*—A notable psychiatric event of 1948 was the International Congress on Mental Health, held in London in August (13) Its program dealt with child psychiatry, medical psychotherapy and mental hygiene. The development of this latter topic utilized an unusual technique: repeated meetings of preparatory commissions, preceding and during the congress, in the attempt to achieve formulations widely acceptable. If the wider world is interested—it showed at the time only slight interest—it can now learn what psychiatrists, in collaboration with other invited participants, have said about world citizenship and the management of international tensions

*Social aspects.*—As another example of the interest and activity of the psychiatrist in broader social dynamics beyond the strictly clinical field is a study by Brodman & Hellman (14) on "The Relation of Group Morale to the Incidence and Duration of Medical Incapacity in Industry." They report that

sults and a formulation of the potentialities for future research. He has found the evaluation difficult because of the lack of "detailed case reports, continued into a respectable period of postoperative observation," with reliable information as to pre-morbid capacities and effectiveness. He offers this pertinent advice.

> If psychiatrists are intent on reporting the therapeutic results of various methods in statistical terms they might well profit by adopting the measures taken by surgeons in studying the results of therapies upon cancer ... The ability to evaluate properly this as well as other psychotherapeutic techniques begs for patience, the development of a more fundamental knowledge of the over-all course of personality disorders, more satisfactory means of stating the outcome of therapy than the presently used grossly noninformative valuative categories; and the insistence of psychiatrists as a group that therapy be judged on a realistic long term basis rather than upon the hurried and preliminary impression immediately following termination of any particular procedure.

The report made by Rylander (3) in the 1947 symposium of the Association for Research in Nervous and Mental Disease and published in the Proceedings provides an excellent example of the careful study of lobotomized patients. The recent report by Lidz (4) indicates that studies of prefrontal functions can gain more by the thoughtful considerations of the interrelationships of psychological test results than by mere routine recording and statistical comparison His study emphasized the importance of a severe limitation in associative range as a determinant of the behavioral disturbance after damage of the prefrontal regions. The report by Heath & Pool (5) of favorable results after bilateral ablation of certain areas of the frontal cortex has aroused much interest in the therapeutic possibilities of this less radically destructive operation.

*Brain physiology.*—Of special physiological interest to psychiatrists is the report by Schiele & Brozek (6) of an "experimental neurosis" resulting from semistarvation in man Thirty-six men recruited from the Civilian Public Service camps had volunteered for these experiments in which the men lost on an average one-fourth of their original body weight All subjects developed emotional and personality symptoms of "semistarvation neurosis " After dietetic rehabilitation the men were back to their prestarvation normal.

One of the physiological problems which has received considerable attention from psychiatrists has been the blood flow through the brain. Fairly clear-cut "negative" findings in schizophrenic patients have been reported by Kety *et al* (7), using the nitrous oxide method of Kety & Schmidt The term "negative" is used in the sense that in 22 schizophrenic patients, no deviations from normal values were found for cerebral blood flow and oxygen consumption. In insulin and electroshock treatments, changes did occur

*Race and mental development*—One problem of much psychological and psychiatric interest has been the analysis of differences in mental development in different racial stocks, a problem much complicated by cultural and

economic differences By its award of the Hofheimer prize, the American Psychiatric Association has given special emphasis to a study by Pasamanick (8) of the personality development of a group of negro infants, who by reason of war-time conditions had approximately the same nutritional conditions as the control white children. Their physical and mental growth, as gauged by Gesell's criteria, were not appreciably different from the controls.

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world-wide collaboration, compromise and public agreement abroad All the other psychiatric activities, care of the mentally ill, psychotherapy, psychiatric research, and so on, should be merely the laboratories where the pathology and and etiology of intra- and inter-human relations are studied, in the interests of prevention of personal and social maladjustment, and in the hope of racial survival.

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different work groups have dissimilar morale, that an individual's work morale is markedly influenced by the group in which he works, and that group morale is intimately related to the occurrence and duration of short medical incapacities.

A different type of interest in social aspects of psychiatry is exhibited in a careful study by Sjogren (15) of the incidence of mental diseases in a relatively static and segregated population. This monograph manifests meticulous care for the consideration of hereditary influences and relatively less interest in group psychodynamics. Very few thorough psychiatic studies of whole populations have been made and Sjogren's data will prove of great interest as a base line for comparisons.

*Miscellaneous.*—The medico-legal problems of psychiatry have aroused in the past much controversial discussion and denunciation. Davidson (16) has recently presented the essentials of several of these problems in an eminently calm and sensible discussion which should be read and studied by all psychiatrists inclined to controversy over legal concepts and practices.

One of the recent publications, outside of psychiatric circles, which has aroused much psychiatric interest has been the "Kinsey report" (17). Reviews of this work by psychiatrists have been on some points appreciative, on others hypercritical, partly on methodological grounds (18) and partly because of concern as to the concept of normality (19).

American psychiatrists will greet with special interest two volumes which have appeared during the past year dealing with personalities of special importance to this professional group. *The Autobiography of Benjamin Rush* (20) has been edited by Corner and published as Volume 25, *Memoirs of the American Philosophical Society. The Commonsense Psychiatry of Dr. Adolf Meyer* by Lief (21) will bring an authoritative version of his views to many who have known them only second hand or in fragmentary form.

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# DISEASES OF BONES AND JOINTS

## Orthopedic Surgery[1]

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### Congenital Deformities

In the treatment of recurrent congenital club foot, Garceau (1) reports the results of transplantation of the tendon of the anterior tibial muscle to the outer side of the foot. The tendon is transposed to the proximal end of the fifth metatarsal or to the cuboid if it is short. Out of 1,275 patients treated for club foot, the procedure was used on 110 feet in 86 patients (6.7 per cent), in whom recurrences had appeared The operation has some corrective effect, but mainly it prevents recurrence after correction is obtained with wedging casts. Excellent or good results were obtained in 91 (83 per cent) of the 110 feet

The etiology of congenital dislocation or subluxation of the hip is discussed by Badgley (2). After extensive embryological studies, he concludes that the condition is not caused by a primary inherited failure of development of a portion of the acetabulum, but is caused by environmental factors extrinsic to the hip joint. It is suggested that an inherited fault in the timing of development may produce these factors.

In the early treatment of congenital dislocation of the hip, Gill (3) notes that excellent results can be obtained in from 25 to 35 per cent and functionally satisfactory results in another 15 to 20 per cent. In the remainder, subluxation or recurrence may be expected. These may be improved by operative treatment. Bost *et al.* (4) report excellent functional results in 60.7 per cent of 112 cases of displasia and dislocation of the hip treated in infancy and satisfactory results in 80 4 per cent. They noted a direct relation between early institution of treatment and good results.

Crego & Schwartzmann (5) in a group of 78 somewhat older patients, obtained normal or near normal hips in 61 per cent, good hips in 31 per cent, and failure in only 8 per cent. They emphasize preliminary skeletal traction for two weeks or more to overcome the shortening, gentle manipulative reductions, fixation in abduction, and internal rotation for three months, then correction of torsion (anteversion of the neck is corrected by a supracondylar osteotomy). The plaster fixation is continued for two months longer, the position of the proximal fragment being maintained by a threaded wire passed through the femur just proximal to the site of the osteotomy. Frankel (6) concludes that an arthrodesis offers the best result as far as pain and fatigue are concerned and recommends this procedure especially for unilateral hips in patients in the lower economic level.

[1] This review covers the period from approximately July, 1947 to January, 1949.

McCarroll (7) found 25 cases of primary anterior dislocation in 111 congenital dislocations of the hip and notes that we have no universally satisfactory method of treating the primary anterior dislocation which cannot be corrected by closed reduction.

From a study of 15 cases of congenital coxa vara, Le Mesurier (8) found that the deformity could not be corrected by heavy traction and is best treated by an inter-trochanteric osteotomy followed by immobilization in wide abduction. This treatment was followed by healing of the defect in the neck of the femur within a year. In early cases which are discovered before the varus deformity is marked, one or two large autogenous bone grafts are placed in the neck of the femur across the defect in the bone. In three instances, this procedure was followed by healing of the defect, and excellent hips were obtained. In a similar study of 15 patients with congenital coxa vara, Bobb *et al* (9) found that subtrochanteric osteotomy with wide abduction converts the shearing force across the femoral neck into a compressing force and promotes healing of the defect In older patients, the condition resembles a fracture of the neck of the femur with nonunion. It has been found that internal fixation with a nail plate aids greatly in maintaining the abduction of the distal fragment.

## Infection

*Pyogenic infection.*—With the advent and availability of antibiotics, there has occurred a marked decrease in the incidence of acute and chronic osteomyelitis because many children with evidence of an acute infection are treated promptly with penicillin and the infection either does not reach the bone or is aborted. Likewise the acute disease is now largely a medical problem and surgery is usually not necessary or is limited to the drainage of abscesses if the penicillin therapy is begun before irreversible changes have occurred in the bone.

In three groups of patients treated by (*a*) emergency surgery, (*b*) delayed surgery, and (*c*) chemotherapy, Nachlas & Markheim (10) found that in the chemotherapy group, there was no mortality, the severity and duration of the disease was decreased, and fewer cases developed recurrence of the local disease or metastatic abscesses. Similar findings were recorded by Altemeier & Wadsworth (11) who studied a series of 71 cases of acute hemotogenous osteomyelitis which were treated with penicillin. In their series, the immediate result of penicillin therapy was striking, the only death being that of a patient who entered in a moribund condition. They emphasize the value of early and adequate treatment and state that such treatment should not be stopped too soon.

Dennison (12), after carefully studying a series of 30 cases of the septicemic type of osteomyelitis treated with penicillin, standardized the treatment as intermuscular injections of 25,000 to 50,000 units every 3 to 4 hr In children from 1 to 12 years of age, the total dosage varied from 200,000 to 450,000 units in 24 hr This procedure was continued for 21 days. The involved extremity was immobilized in traction or splints; and if pus was

present on admission, the abscess was aspirated or incised and then sutured (100,000 units of penicillin was injected into the cavity). In 6 cases in which pain, tenderness, and toxemia were not relieved in 24 hr., the bone was drilled with dramatic relief from pain. Immobilization was continued until the danger of pathological fracture was past. Chronic osteitis was treated surgically under an "umbrella" of parenteral penicillin.

Several papers were published on the management of chronic infection secondary to compound fractures resulting from war injuries In one of these papers Reynolds & Zaepfel (13) emphasize the use of the split-thickness skin grafts for temporary or permanent closure of wounds which cannot be closed after debridement and saucerization. They believe that delayed primary closure of these wounds will lessen hematoma formation and will give a higher percentage of recoveries.

In a series of 25 cases of severe chronic osteomyelitis which had been draining for an average of 19 months in spite of many forms of treatment, Wilson (14) was able to obtain healing in 21 cases by radical sequestrectomy after adequate preoperative preparation and treatment before and after operation with streptomycin and penicillin.

An important contribution to the prevention of infection in bone was made by Davis (15) in his paper on the primary closure of compound fractures After a careful debridement, the fracture is reduced accurately and immobilized by internal fixation when advantageous. The wound is then closed using relaxing incisions and split skin grafts if necessary A voluminous pressure dressing is applied and the extremity is immobilized in a plaster cast Penicillin, blood transfusions, and a high protein diet are used.

*Tuberculous infection.*—In the treatment of tuberculous joints by amputation, Bosworth & Graul (16) find that such an operation offers little hope of saving the life of a patient if he has an active pulmonary lesion, but nevertheless, it may be advisable because it relieves the severe pain. The best results are obtained when the amputation is performed relatively early, in order to remove an extremity which is incurable or which will be worthless when cured In 27 cases reviewed, death occurred in 17 or 63 per cent.

In an analysis of 177 patients operated upon for Pott's disease, Bosworth & Levine (17) found that the mortality rate was 37.3 per cent, while that in 240 such patients not operated upon was 69 6 per cent. Children progressed unfavorably under conservative care, but showed marked improvement after surgery; and negroes progressed as favorably as whites when given adequate care. Amyloid disease accompanying tuberculosis of the spine was practically always fatal.

In a series of 28 children requiring arthrodesis of the hip (23 for tuberculosis) Pease (18) found no postoperative deaths, but three children died from one to two years later of tuberculosis meningitis. Fusion failed in only three cases, and these were fused by subsequent operations. The method employed was the combined intra- and extra-articular operation of Chandler (72) Preliminary obturator neurectomy was performed in six cases, and it is suggested that this may aid fusion.

In Sweden, Ahlberg (19) studied a group of 113 cases of tuberculosis of the hip which had been operated upon by intra-articular resection of the diseased tissue. There were five postoperative and three subsequent deaths. Fusion occurred in 58 cases and failed in 40. In a similar series of 50 cases, Dobson (20) noted a mortality of 2 per cent and satisfactory fusion in 87.5 per cent. The extra-articular iliofemoral graft was preferred, and this method was used in most of the cases. Brittain (21) describes his ischiofemoral method for arthrodesing the hip and states that in 38 patients with tuberculosis of the hip, 32 were successfully fused by 38 operations.

McCarroll & Heath (22) emphasize the secondary changes of shortening, atrophy, and relaxation of the ligaments of the knee which occur in children who have been subjected to prolonged conservative treatment (average, four years) for tuberculosis of the hip before fusion was attempted, and they suggest that even in young children, an attempt be made to fuse the hip after not more than six months of conservative treatment. At present, they prefer the Brittain ischiofemoral arthrodesis. (In this operation, the femur is divided obliquely below the trochanter, and a massive tibial graft is driven through the osteotomy site into a slot in the ilium just below the acetabulum.)

By the use of positive pressure, Charnley (23) has been able to secure firm fusion in the knee joint between the tibia and the femur in a remarkably short time (four weeks). The reviewer has used this method for several years,

approximated by turnbuckles or clamps, thus pressing the ends of the bones together.)

A limited experience indicates that the results of the surgical treatment of bone and joint tuberculosis will be further improved by the use of streptomycin, but it seems probably that it will still be necessary to fuse tuberculous joints by operation in order to arrest the disease permanently; this is especially true of adult patients.

## Chronic Arthritis and Allied Conditions

Hench *et al.* (24) have reported remarkable improvement in the clinical condition of patients suffering from rheumatoid arthritis after the daily injection of a hormone of the adrenal cortex (Compound E) and of pituitary adrenocorticotropic hormone. After the daily injections were discontinued, the symptoms usually, but not always returned promptly. Unfortunately, these materials are so rare that they can only be used in a few selected patients. It is to be hoped that this condition will be remedied in the near future and that the early promises of this form of therapy will be fulfilled in a wider experience.

The satisfactory surgical treatment of chronic osteo-arthritis of the hip (malum coxae senilis) is still one of the unsolved problems which is frequently encountered by orthopedic surgeons. Smith-Peterson (25) describes the evo-

lution of his operation in which a new hip joint is formed around a vitallium mold. He reports that in a series of 500 such arthroplasties of the hip, 90 were performed for malum coxae senilis and that in these cases, the results were more satisfactory than those obtained by arthrodesis. The patients had a limp, but it was painless; and they were able to lead an active life and to put on their own shoes and stockings. Law (26), in a critical review of 150 of Smith-Peterson's cases, found that of 16 operations for malum coxae senilis, the results of 15 were satisfactory to the surgeon and to the patient. The range of movement varied from 73 to 100 degrees; and while the limbs presented some shortening and weakness, the patients were relatively free from pain and used a cane only for distance walking. Stinchfield & Carroll (27), in a study of forty-five vitallium cup arthroplasties of the hip, found that of nine performed for chronic arthritis, the results with regard to motion were good or very good in five, and that six patients had little or no pain.

Brittain (21) reports that he obtained fusion in 45 hips after operation by his ischiofemoral method of arthrodesis on 52 patients. One patient died of pulmonary embolism eight days after operation. The principal objection to the use of this and other methods of arthrodesis in older patients is that after the operation, a double plaster spica is applied and maintained for at least four months or until fusion is solid. This prolonged postoperative fixation in a plaster cast has been avoided by Dixon (28) who combines the Watson-Jones operation of fixation by a long Smith-Petersen nail driven up through the neck and head of the femur into the ilium with an intra- and extra-articular arthrodesis. No immobilization other than the nail is used, and the patient is permitted to get up on crutches in about four weeks Use of the crutches is continued until the hip is solid. Fusion was obtained in all of ten patients operated upon in this manner.

In efforts to relieve the pain and improve the function of the joint by a relatively minor operative procedure which does not require a postoperative fixation entailing a prolonged convalescence, Kaplan (29) and Key & Reynolds (30) have sectioned the obturator nerve, thus removing part of the sensory supply to the hip joint and partly paralyzing the adductor muscles. Kaplan sectioned the nerve in the thigh and Key & Reynolds sectioned it in the pelvis. The results seem to be about the same In over 65 per cent of the patients, the decrease in the pain which resulted was considered sufficient to justify the procedure, and the weakening of the adductors did not cause important disability Mulder (31), on the other hand, states that he has abandoned the operation because in his clinic the results were good in 11, fair in 15, and poor in 22 of 48 patients on whom obturator and sciatic neurectomy were performed for the relief of pain and disability caused by osteo-arthritis of the hip

Bateman (32) reports satisfactory relief of pain after denervation of the elbow joint in ten patients with post traumatic arthritis of the elbow. The ulnar, median, radial, musculocutaneous, and anconeus branches were exposed, and the articular branches from these nerves were severed.

The results of arthroplasties of the knee have been reviewed by Samson

(33) and Speed & Trout (34), and the results reported in each paper are sufficiently good to warrant continuance of the operation in selected cases. The favorable cases are those adults under 50 years of age who are not laborers, with bony or fibrous ankylosis of the knee from acute infectious arthritis (especially gonorrheal arthritis), suppurative arthritis without osteomyelitis, or trauma. With the wider use of chemotherapy and penicillin, the number of cases of ankylosis following acute infectious arthritis is greatly reduced; and the patients in whom an arthroplasty of the knee is indicated are relatively rare Charnley (23) (and the reviewer) would usually prefer an arthrodesis in those patients in whom a bony ankylosis in satisfactory position is not present. There is no question that the ankylosis of the knee gives a more painless, rugged, stable, and durable extremity; but some patients, usually women, are willing to sacrifice some of the above qualities in order to obtain movement. More than 90 degrees of movement should not be attempted as this leads to instability.

Arthrodesis of the ankle is being performed more frequently as it becomes more widely known that excellent function of the extremity may be expected if this joint is fused with the foot in a position of slight equinus Gallie (35) has described a method of fusion in which cortical grafts from the tibia are placed on either side of the body of the astragalus after the cartilage here and on the inner aspects of the malleoli has been removed. Adams (36) exposes the ankle by removing the distal three or four inches of the fibula and prepares it for a graft by splitting off its inner cortex. The articular cartilage is then erased from the tibia and the astragalus, and a bed is prepared for the graft by freshening the lateral aspects of the tibia and astragalus Small spaces between the bones are filled with bone chips, and the graft is applied across the joint and fixed with three screws (two in the tibia and one in the astragalus). A cast is applied with the foot in slight equinus and weight bearing is begun in a few weeks. The cast is removed in twelve weeks and the stability of the joint is tested. Either method may be expected to be successful in a high percentage of cases.

The subject of synovectomy is reviewed by Pardee (37), and the theoretical and practical effects of the operation are discussed. In 48 knees in 40 patients, it was noted that the percentage of excellent results decreased from over 60 per cent during the first year to 20 per cent after five years The good results, however, increased during the same period from 20 per cent to over 60 per cent. Thus, the results were poor in less than 20 per cent of the entire series; and it is believed that the operation should be continued in selected cases.

The subject of chondromalacia of the patella has been receiving increased attention during the past few years, and it is now widely recognized as one cause of chronic pain and disability in the knee. The subject is reviewed by Bronitsky (38) and the symptomatology, pathology, and operative treatment are described. From a series of 29 cases operated upon, it is concluded that the entire patella should be removed if the degeneration of the cartilage

is extensive; and chondrectomy (shaving off of the locally degenerated cartilage) is reserved for the relatively mild cases. Patellaplasty (removal of all cartilage and subchondral bone with a saw) and chondrectomy with attempts to cover the raw surface with synovial membrane, gave consistently poor results; and these operations have been abandoned.

The calcium deposits which occur in the tendons of the rotary cuff of the shoulder in the floor of the subdeltoid bursa have been studied by Key (39) and compared with similar deposits which occur in the vicinity of other joints, usually in tendinous insertions or in ligaments. It is noted that the symptomatology, clinical course, x-ray appearance, microscopic pathology, and response to treatment of the deposits which occur in the shoulder are similar to those of deposits which occur around the various joints in the body. The deposits may exist for an indefinite time and cause no symptoms, and they may disappear spontaneously or become inspissated and chalk-like in character and remain indefinitely. Likewise they may, for some unknown reason, become acutely inflamed and very painful. This pain may subside after a few days or may persist for weeks or months. Relief may be obtained after treatment by deep x-ray therapy, by multiple puncture of the focus, or by incision and light curettage. It is emphasized that the foci are usually multiple, and that it is not necessary or even advisable to attempt to remove all of the calcium. In a very acute case with severe pain and disability, the operative treatment offers the best chance of a rapid and permanent cure.

In the group of stiff and painful shoulders without calcification which are variously termed periarthritis of the shoulder, subdeltoid or subacromial bursitis, adhesive capsulitis, scapulohumeral periarthritis, Duplay's disease, etc , Hitchcock (40) has studied especially the casses in which the condition is caused by inflammation in the tendon sheath of the long head of the biceps. He believes that a prominent supratubercular ridge or an unusually shallow bicipital groove are conditions which tend to increase the mechanical difficulties under which the biceps tendon functions and to predispose it to the development of tenosynovitis in this tendon sheath. He has devised an operation in which the intra-articular portion of the tendon is excised, and the stump of the distal segment is fixed in the bicipital groove.

## Low Back Pain and Sciatica

In the literature on low back pain and sciatica, lesions of the intervertebral disc occupy an increasingly prominent place; and in a symposium (73) before the American Orthopedic Association, the end results of operations for the removal of intervertebral discs were reported. Lenhard (41) investigated a series of 843 operations performed by Dandy and found that good results were obtained in 67.5 per cent of 147 patients who returned for examination and in 59 5 per cent of 336 patients who responded to questionnaires by mail. The poor results (not improved) in the two groups were 15 5 per cent and 17.6 per cent, and the balance were improved. Twenty of the 147

patients who returned for examination had had two or more operations Spinal fusion was not done in any of these patients, nor were they subjected to myelography before operation.

In a series of 234 cases (102 with and 132 without spinal fusion) Barr (42) found that of the cases with spinal fusion, 60 per cent had no back pain and 73 per cent had no leg pain, while of those in whom the disc was removed and the spine not fused, the results were 45 and 58 per cent respectively. The percentage of poor results was the same in each series, 10 per cent. Barr believes that with improvement in technique, fusion operations will be developed which will not cause undue increase in the operative risk or prolongation of postoperative convalescence, and that spinal fusion will then be a routine part of the disc operation.

In a series of 1,217 patients operated upon at the Mayo Clinic and reported by Love (43), 1,087 or 81 per cent were traced by interview or questionnaire; 53.7 per cent were relieved, 36.7 per cent had partial relief, and 9 6 per cent had no relief; 64.4 per cent were doing the same type of work they did before operation

In a series of 182 discs removed from 166 patients Eckert & Decker (44) found that it was not possible to correlate the pathological condition of the material with the herniated, bulging, or softened disc noted at the operation. The pathological changes resembled those which occur with advancing age. These were· extension of nuclear tissue into cartilaginous plates, vascularization of this defect, scarring and vascularization of the annulus. The nucleus showed degeneration of the stroma in 49 per cent of the cases The clinical results were investigated by questionnaire and showed complete relief in 32.2 per cent, moderate relief in 54 5 per cent and no relief in 13 3 per cent Eckert & Decker were not able to correlate the pathological findings with the clinical results.

Iman & Saunders (45) divide patients with low back pain and sciatica into three groups. (*a*) those with backache and local signs of injury to vertebral structures and deep radiating pain down one or both extremities (these patients have ligamentous injuries and should be treated by immobilization and support), (*b*) patients with symptoms identical with those of group (*a*) plus evidence of nerve root compression (these patients should be treated by relief of the nerve root pressure, and in addition, the injured ligamentous structures should be protected), and (*c*) those in which backache is mild or absent and symptoms of nerve root compression are prominent (these symptoms suggest spinal cord tumors, the removal of which is indicated; support to the back is not necessary).

Steindler (46) notes that the disc has few, if any, sensory fibers and that the adjacent ligamentous structures are richly supplied with sensory elements With degeneration of the disc, stress is placed upon the ligaments and muscles. Eventual herniation into the spinal canal may occur as a late result. He recommends conservative trial treatment in all cases. If this fails, the disc is to be removed by a conservative laminectomy which is to be

followed by spinal fusion. The reviewer, in a paper (47) published a few years ago, and which has provoked considerable comment, stated that in the great majority of patients with idiopathic low back pain with or without sciatica, the symptoms are caused by lesions of intervertebral discs in the lower lumbar spine. Further experience and observations have strengthened the above conclusion, and he believes, that the facets, ligaments, bones, and muscles play a relatively small part in the production of low back pain and sciatica. The important structures are the discs and the nerve roots. It is probable that those failures of operative cure, which occur in patients who are not neurotic, are due to postoperative irritation of the nerve roots from additional protrusion of disc material, or from adhesions or inflammation in or around the nerve roots. If this is true, we should improve our technique of disc removal and then spinal fusion will be necessary in a very small percentage of these cases

As a result of a study of 151 cases operated upon, Caldwell & Sheppard (48) state that there are no criteria for spine fusion following removal of a protruded nucleus pulposus, with which the reviewer agrees Not only do we not know which spines should be fused, but we have not found that fusion can be depended upon to relieve patients who were not relieved by removal of the protruding disc

In a series of experiments on dogs by Key & Ford (49), the intervertebral discs were subjected to: (*a*) puncture with a 21 gauge needle, (*b*) incision with a small tenotome, (*c*) incision and light curettement, and (*d*) incision and heavy curettement. The spines were then studied at intervals of from 2 days to 28 weeks. The vertebral bodies did not fuse, but a cavity persisted in the disc and the annulus healed. In some cases, there was definite protrusion of nuclear material into the spinal canal. In all cases there were adhesions of the nerve roots to the incised and curetted discs. It was believed that a weakening of the posterior portion of the annulus which might be due to degenerative changes or injury is the primary lesion in intervertebral disc protrusions and that the degenerative changes in the nucleus are secondary.

In a series of 28 patients with a clinical diagnosis of displaced lumbar intervertebral discs supported by positive myelograms, Colonna & Friedenberg (50) found that after conservative treatment by bed rest, traction, sedation, daily physical therapy, and a back support, 29 per cent were free from pain, 39 per cent were improved and 32 per cent were still disabled. These results are not as good as were those obtained in a series subjected to operation

In an effort to improve the results from operative spinal fusion and to shorten the period of postoperative immobilization, King (51) excised the cartilage from the apophyseal joints and placed screws through these joints

slowly while the patient was ambulatory. McBride (52) denudes the apophyseal joints of cartilage, then distracts the laminae and mortises a graft of autogenous bone (spinous process) across the apophyseal joints. Fusion is believed to have occurred in all except 5 of 41 cases subjected to this operation.

Thompson & Ralston (53) found that failure of fusion occurred in 15 6 per cent of 376 patients who were operated upon by the Hibbs method for scoliosis and in 13.9 per cent of 430 patients who were subjected to a lumbosacral fusion for low back pain. Of 49 patients in whom the spine was fused from the fourth lumbar to the sacrum by internal fixation with screws across the joints, pseudarthrosis occurred in 27, or 55.1 per cent; and in five, or 12.2 per cent, of 41 patients with lumbosacral fusion. In 65 cases with spondylolisthesis, the number of failures of fusion was nine, or 13.8 per cent. Of the entire series of 1,096 patients, failure occurred in 16 6 per cent.

In a similar study by Cleveland *et al.* (54) of 674 operative procedures for lumbosacral spinal fusion in 594 patients, pseudarthrosis occurred in 119, or 20 per cent. The incidence was only 3.4 per cent when only the fifth lumbar was fused to the sacrum, but rose to 17.4 per cent when the fourth was included, and to 33.3 per cent when the three lower lumbar vertebrae were fused to the sacrum. It is concluded that the possibility of failure of fusion should be discussed with the patient before operation in order that he may be forewarned and that consent for repair may be obtained more readily. Also, one should avoid fusing any more vertebrae than necessary. It is further stated that the success or failure of a fusion operation should be judged by biplane roentgenograms taken with the patient in flexion and extension, and with right and left bends, and that even then, a few cases of pseudarthrosis will be missed

## Bone Grafts, Bone Union, and Fractures

Abbott *et al.* (55) present the results of an extensive clinical and experimental study of the relative value of cortical and cancellous bone in various types of bone transplant procedures. They conclude that the mature elements of either a cortical or a cancellous graft seldom survive transplantation and that the elements which may survive and produce new bone are the endosteal and periosteal layers. A cortical graft is a solid mass of mature elements with endosteal and periosteal surfaces Cancellous bone on the other hand, is a mass of interlacing and branching trabeculae, each of which is covered by endosteal cells.

Cortical bone is most useful where strength is of primary importance, and its osteogenic power may be reinforced by the judicious use of cancellous bone Cancellous bone alone is used to fill defects in a bone, to stimulate arthrodesis and union in fractures near the ends of bones, and in spinal fusions. Bone defects in long bones are best bridged by cortical grafts plus cancellous bone. It is noted that cancellous bone grafts possess a high degree of viability and, when protected by the use of penicillin, are quite resistant

to infection, while cortical grafts under the same conditions are usually extruded as sequestra. These authors advise that many bone grafting operations are best performed in stages, and this is good advice.

Boyd and Fox (56) report the latest results of massive bone grafting for congenital pseudarthrosis. Of seven cases in which 10 massive bone grafts were used, bony union occurred in all but one. It is recommended that two massive tibial grafts be taken from a parent and that these be placed on either side of the atrophic bone so that they serve as a clamp to fix the fragments, and that cancellous bone be placed between the grafts Splintage is continued until a new medullary canal is established. In three cases refracture occurred. Two of these were grafted successfully, and the other was amputated. It is believed that grafts from a bone bank would be suitable for this procedure.

At the present time, many orthopedic services possess a bone bank and use homogenous preserved bone in a wide variety of operations. In most instances, the material is excess bone removed in the operating room in the course of surgical procedures on clean wounds. It is collected under aseptic conditions and stored in sealed containers in a refrigerator at $-2°$ to $+5°$C. for three weeks or indefinitely at $-25°$C. in a deep freeze unit as recommended by Bush (57). This bone is especially useful in filling defects and in spinal fusion.

In our clinic, we use bone which is preserved in 1 to 2,000 aqueous solution of merthiolate for two weeks and then in 1 to 5,000 solution of merthiolate until used. The jars containing the bone are kept in an ordinary refrigerator By using the relatively strong antiseptic solution, we are able to use bone from thoracoplasties, amputated extremities, and even necropsies. In only one instance in the past two years has a positive culture been obtained from the bank, and this is believed to have been an airborne contamination. This method, some results of its use, and studies on the fate of the preserved bone were presented by Reynolds & Oliver (70) at the 1949 meeting of the American Academy of Orthopedic Surgery. We believe that the bone preserved in an antiseptic solution is especially suitable for filling cavities in bone which have been infected, because there is enough merthiolate in the material to discourage its invasion by pathogenic bacteria.

A similar extensive study of the results of the use of refrigerated bone in orthopedic surgery was presented by Wilson (71) at the 1949 meeting of the American Orthopedic Association In both papers, examples were given of the successful use of preserved bone in numerous different types of operations, and the resultant saving in further incisions and trauma.

That homografts may be useful in orthopedic surgery is also demonstrated by Henry (58), who used homograft chips from other members of the family to fill large cavities left after the removal of a giant cell tumor in one patient and a bone cyst in another. In another case, massive tibial homografts from a brother were used to splint the tibia of a congenital pseudarthrosis, after the method of Boyd, and the fracture united.

The technique of bone grafting is greatly simplified by the onlay method of Phemister (59), who places an autogenous onlay graft of cortical bone subperiosteally across the site of the nonunion. The graft is not fixed by screws, wire, or sutures, but is held in place by the soft tissues when the wound is closed. This method is especially useful in cases where the bone fragments are in a satisfactory position and are united by fibrous tissue. The fibrous tissue between the fragments is not disturbed. In cases which have been infected, this form of grafting can be done with safety relatively soon after the wound has healed.

Nonunion of the neck of the femur is still a problem which has not been satisfactorily solved. Gill (60) recommends arthrodesis when other operations are contraindicated or have failed. In his cases, bony ankylosis was obtained in only 60 per cent of the patients, but the other 40 per cent had stable and useful hips and did not complain of pain.

Krida (61) performs the Whitman type of reconstruction in which the the head is removed, the stump of the neck is inserted into the acetabulum, and the trochanter is transplanted downward onto the shaft of the femur. The difficulty with this operation is that it is not reliable and does not always result in a painless hip.

Wilson (62) separates the trochanter from the shaft, then the head of the femur from the acetabulum, and after mobilizing the proximal end of the femur, trims off the neck and fits a vitallium cup over the trochanteric end of the bone. This is then placed in the acetabulum, and the trochanter is reattached farther down on the shaft of the bone. In a somewhat similar procedure, Moore (63) removes the head of the femur and with an electric burr hollows it out until it is translucent He then fits this cartilaginous cup over the rounded proximal end of the shaft and replaces it in the acetablum, thus performing a cartilaginous cup arthroplasty By this method, he has obtained satisfactory hips in 10 of 11 cases operated upon.

A high osteotomy, just above the lesser trochanter with an angulation of 60°, is performed by Dickson (64), the stump of the shaft is then brought out against the lateral side of the proximal fragment and fixed with a blade plate. This results in a valgus shift of 60° in the angle of the neck of the femur and changes the shearing force at the site of the nonunion to a compressing force. It also tends to lengthen the extremity about one inch. Preliminary traction is used if necessary to pull the shaft down into position, the 60° osteotomy is marked with a semihexagonal chisel, and the bone is then severed with a thin osteotome

In an effort to lessen the percentage of nonunion and of aseptic necrosis of the femoral head after intracapsular fractures of the hip, Patrick (65) fixes the fragments with a Smith-Petersen nail and then places an autogenous fibular graft above and parallel to the nail He reports 87 per cent union and only 9 per cent of aseptic necrosis in his cases. We have used preserved (bank) bone in a similar manner and believe that is it beneficial.

In an effort to prevent nonunion in fractures of the long bones which

have been subjected to internal fixation, Eggers (66) has advised an internal contact splint, which is a bone plate with slots instead of round holes for the screws. When properly applied, this splint enables the muscle tone to pull the fragments together and stimulate union while the splint maintains position and alignment.

The intramedullary nail for the internal fixation of fractures of the long bones, expecially the femur and the tibia, is now looked upon with favor in many quarters. The triangular or clover leaf nail of Kuntscher is preferred in most clinics [Boehler & Boehler (67)]. However, Ehrenhaft & Tidrick (68) prefer the heavier diamond shaped nail of Hansen & Street (69). In a series of ten pathological fractures, Ehrenhaft & Tidrick found that the use of the long medullary nail permitted early mobility of the extremity, relieved pain, reduced the nursing care, and shortened the period of hospitalization.

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# DISEASES OF THE RESPIRATORY SYSTEM[1]

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Chemotherapy remains the subject absorbing much of the energy and attention of chest research, and the past year has seen an advance in the development and application of new antibiotics as well as a better understanding of the old. Other areas of research, however, have also yielded substantial advances in medical techniques, although they have not, perhaps, been so spectacular. Cytologic studies of sputum, for instance, promise a most noteworthy addition to the armamentarium against cancer. New surgical techniques appear to offer radical cure to patients who, a short time before, would have been deemed hopeless. Statistical studies of large-scale use of BCG vaccine are now available and should contribute to a definitive evaluation of that agent.

There seems a tendency generally toward consolidation of our new knowledge and better organization in the diagnosis and treatment of chest diseases. Interest is increasing in pathology and consequently there is a developing understanding of disease processes, less effort toward formulating classic processes as a basis for diagnosis, and more effort toward refining specific diagnostic techniques. A significant development is the new position of the laboratory; it is more and more apparent that in any serious condition the final diagnosis must be based on laboratory studies. On the other hand, treatment tends to be standardized and simplified.

Great advances have been made in surgery; intratracheal anesthesia and curare have become standard procedures whenever the chest is to be opened and have greatly decreased operative and postoperative mortality. The administration of whole blood continuously during the operation has had the effect of de-emphasizing the question of operative risk; recently a chest surgeon was able to state that "any patient is suitable for chest surgery"

## Penicillin

There has been real, if not spectacular, progress in the shaking-down of the older antibiotics, as well as in standardization of their use. Penicillin, with the advantage of low toxicity in high dosage and relatively prolonged effectiveness, is the preferred agent for most gram-positive infections of the chest, and is largely responsible for the reduced incidence of empyema and secondary infections. Standard dosage for adults is 300,000 units of penicillin G upon diagnosis, followed by an intramuscular injection of 25 to 50,000 units every three hours Development of dosage forms for penicillin which will make less frequent injections practicable is going forward, although there remains an understandable reluctance to adopt a new treatment merely because of convenience

[1] This review covers the period from approximately August, 1948 to August, 1949.

The chief new application of penicillin has been to the fungus diseases Nichols & Herrell (38) found that a heavy dosage, 500,000 units daily for a period of six weeks, apparently permanently cured actinomycosis infection on the basis of 46 cases followed from one to five years. Campbell & Bradford (5) found both penicillin and sulfonamides effective in the treatment of extensive actinomycosis of the thorax and abdomen; Kay (29) found penicillin alone or combined with sulfadiazine to be most effective Penicillin also proved successful against the rare fungus streptothrix in an unusual case reported by Schafer (55). It is worthy of note that remission was accomplished with a dosage of 40,000 units every three hours after 20,000 units had proved ineffective, in line with previous studies establishing the effectiveness of penicillin in large doses in instances where smaller quantities have been as completely ineffective.

The administration of drugs in aerosol form has been established as a primary technique in the treatment of lung infections. Potter (46) points out the readiness with which penicillin used as an aerosol passes into the blood stream, although effective concentrations can exist in the bronchi even when penicillin is almost undetectable in the blood.

In instances where clinical techniques do not provide adequate criteria,

This is the addition of staphylococcus aureus cultures diluted to one-tenth, refrigerated for 24 hr., and placed in Petri dishes with solid agar medium. The sputum or secretions are placed on the surface of the agar with a platinum ring. After another period of 24 hr. of refrigeration, the zone of inhibition of the culture is regarded as a measure of the antibiotic action Farinãs and his associates found that a zone of inhibition of 24 mm. corresponded to 100 units of antibiotic in each 100 cc of material examined

There has also been some attempt to answer questions generally asked about the effectiveness of aerosols. Detergents, or wetting agents, which break up cellular agents, thus insuring better contact with bacteria, are now used as solvents. Sprays that break up the liquid into particles of two microns diameter are available and permit more effective penetration. When certain areas of the lung have lost their function with consequent increase in the percentage of residual air in such areas, still more effective results with aerosols may be possible with techniques of more direct application.

Some useful studies of antibiotics in the pleural cavity may be cited. Neither penicillin nor streptomycin, according to de Parterarroyo & Franco Morante (42), and Beattie, Blades & Horton (2), irritates the pleural surfaces, and thus they do not cause adhesions. Both drugs were found to pass readily into the blood stream from normal pleural surfaces. However, inflammation greatly inhibits such absorption, in the treatment of empyema, evidence that the antibiotic is passing from the pleural surfaces into the bloodstream is an indication of the clearing of the infection. It must be noted, however, that neither penicillin nor streptomycin passes readily from the

bloodstream to the pleura; hence, treatment with either of these drugs must be direct. Aureomycin, on the other hand, does pass from the bloodstream to the pleural fluid, as demonstrated by Herrell & Heilman (27), and will gain application because of this fact.

Penicillin and the sulfanomides have in general answered the problems of gram-positive infections, and most of the attention of research has been directed toward gram-negative and virus infections. However, in spite of the feasibility of heavy doses, penicillin-resistant strains of gram-positive organisms continue to develop. Hirsh & Robinson (28) report such developments in 14 of 75 patients with bacteremia. One strain of Type 1 pneumococcus was found to be penicillin resistant but most of the resistant organisms were streptococci. *Staphylococcus aureus*, however, apparently develops resistance most readily.

### Aureomycin

Nichols & Needham (39) found that penicillin resistant staphylococcal infections responded in four cases out of six to aureomycin That this drug will be increasingly useful is indicated by the findings of these authors on the development of penicillin resistance Administration and dosage have not yet been standardized, but Nichols & Needham found in six patients that intravenous administration of 200 to 500 mg. in 250 cc. of physiologic saline solution caused least discomfort. Oral administration of 500 mg., 750 mg., or 1.0 gm occasioned nausea and vomiting in three patients of six.

Aureomycin promises further effectiveness against some viruses, particularly in connection with atypical pneumonia In 13 consecutive cases diagnosed as atypical pneumonia, Schoenbach & Bryer (56) administered aureomycin. Ten had previously failed to respond to penicillin and/or sulfadiazine. All patients were afebrile in 24 to 48 hr and recovered without further complications Primary atypical pneumonia is diagnosed largely by exclusion, but this series seems convincing Kneeland, Rose & Gibson (30) reported another series in which eight out of ten had typical cold agglutinins In nine patients the temperature became normal within 12 to 48 hr after administration of aureomycin was begun Neither set of cases revealed any important toxic effects connected with the administration of the drug

Steenken & Wolinsky (57) tried aureomycin on tuberculous guinea pigs, they employed a dosage from 0 2 mg to 1 6 mg, the latter being near the maximum tolerable, but could discern no deterrent effect on the course of the disease.

That there is no piling-up effect following multiple doses of this antibiotic is suggested by the studies of Herrell & Heilman (27) on the absorption, diffusion, and excretion of aureomycin. They found that aureomycin diffuses readily through the placenta, into the cerebrospinal fluid, and into the pleural fluid.

### Streptomycin

Streptomycin therapy has developed importantly in the past year. Its proven effectiveness against tuberculosis seems to have overshadowed its

usefulness against other organisms. Pulaski & White (48) have made important though not conclusive trials of streptomycin against a variety of organisms. Among 44 patients treated for various respiratory infections, they found that the drug was effective in varying degrees in penumonia due to *Klebsiella pneumoniae*, and pneumonia in which *Hemophilus influenza* was implicated, they also indicate the use of streptomycin for pleuropulmonary tularemia. Patients with coccal pneumonias should be treated with streptomycin only after trial of other chemotherapeutic agents. One patient treated with streptomycin and penicillin survived pneumonia with seven days of agranulocytosis. On the other hand, it had no effect on the course of pertussis with bronchopneumonia in two patients and was of no value in the treatment of one patient with atypical pneumonia. Upon treatment with streptomycin, one patient with blastomycosis sustained remission only while under treatment, and a patient with moniliasis showed no improvement.

Streptomycin has now been used against tuberculosis in a large enough number of cases to make evaluation possible. The most detailed study so far has been that of Pfuetze & Pyle (45). In extrapulmonary forms they found consistent remission in generalized miliary tuberculosis without meningeal involvement, in a sizable number of cases, the process remained arrested for two years after termination of treatment In disseminated forms of tuberculosis, the success of treatment will be gauged by the results at two, three, and five year intervals.

Streptomycin therapy, note the authors, is accepted as the most effective treatment for ulcerative and granulomatous lesions of the oropharynx, larynx, and tracheobronchial tree; the lesions heal completely after a few weeks, and there is only a small percentage of recurrence Pfuetze & Pyle (44) find streptomycin of little effect against tuberculous pleural fistulas, but this conclusion is by no means as decisive as some of the other findings cited above.

The measure of usefulness of streptomycin in pulmonary tuberculosis depends upon the extent to which the drug can come in contact with the bacilli It is thus often spectacular in instances of early acute and subacute lesions. This is clearly brought out in the series of Riggins & Hinshaw (50) On the other hand, it will usually be of little effect if there are sizable cavities or large areas of necrosis or caseation

Another limitation arises from the apparent rapidity with which the tubercle bacilli acquire resistance to the drug. Acquired streptomycin tolerance has been studied by Pyle (49) who found that patients under treatment with streptomycin may at times discharge tubercle bacilli several thousand times more resistant to the drug than the usual strains. Further research is indicated by the findings of Fisher (17) that streptomycin resistance in *in vitro* studies varies with the media used, Youmans media produced twice as many resistant strains as Dubos-Davis media That Pyle's explanation of acquired resistance is not the complete one is suggested by the finding in 1947 of the development of streptomycin-dependent strains. This is confirmed by the study of Lenert & Hobby (31), in which streptomycin strains resistant *in vitro*, became after *in vivo* passage, to some degree dependent.

Dosage of streptomycin has not been fixed; against the earlier view that a maximum tolerable dose was desirable, many specialists handling the drug frequently now use a relatively small dose of around 0.5 gm. to 1.0 gm. a day. Riggins & Hinshaw (50), on the other hand, found that larger daily doses appeared to bring out more frequent and marked improvement than the smaller ones, where the reaction was not minimized or nullified by severe toxic reactions.

In general, it seems that early tuberculosis should be attacked immediately with streptomycin. In chronic tuberculosis, it is frequently most useful in controlling the periodic exacerbations by which the disease progresses. However, in view of the resistance developed so markedly by the tubercle bacilli toward streptomycin, care should be exercised in its indication, only after treatment with penicillin and other drugs has been attempted should streptomycin therapy be undertaken (7). Where cavitation is present, it may be useful in clearing bronchial lesions in preparation for surgery. Where surgery is contemplated, it seems effective in preventing spread (12).

The neurotoxic potentialities of streptomycin have been apparently overcome with the development of dihydrostreptomycin. Its antibacterial activity usually parallels that of streptomycin, and since it has been claimed to be significantly less neurotoxic, it has been given in larger doses and for more prolonged periods; it was reported that some patients showing allergic reactions to streptomycin have been able to continue with the dihydro-form. However, late unpublished reports have not entirely supported the claims of lessened toxicity

One of the lesser known antibacterial drugs is the antibiotic streptothrycin, which is obtained from actinomycetes. It has proven effective in inhibiting multiplication of tubercle bacilli *in vitro* In a comparative study of streptothrycin with other antibacterial substances, Wagley & Steenken (60) found that streptothrycin inhibited the growth of the tubercle bacilli H37RV and H37Ra, as well as *Mycrobacterium phei*. In the concentrations employed it was more bacteriostatic than tryothrycin, 4, 4'-diaminodiphenylsulphone, promin and diasone. No definite information on its clinical value is available at this writing, presumably because of its toxicity.

Pfuetze & Pyle (45) made a clinical analysis and comparison of the various antibacterial agents. Streptomycin in conjunction with the surgical treatment of tuberculous is, they indicate, its most important use. Their experience with streptomycin confirmed what has long been suspected, that some lesions will not respond to any type of chemotherapy. In a number of selected cases, promin was found to be effective and although acting more slowly than strepomyocin, appeared to exert its effect during administration periods of as long as two years. The authors conclude that the potential toxicity of promin has probably been exaggerated; the average tolerance for the drug is a daily dosage of 0.8 gm. extending for nearly a year. There is some subjective evidence of toxicity, such as anorexia, nausea, headache, and insomnia, and the most common objective evidence is a propensity for promin to cause a hymolytic anemia.

The authors note that diasone is decidedly inferior to promin in effect, and they found that promizole, which is practically nontoxic can be tolerated in large doses, as much as 10 to 15 gm. a day.

Experimental and clinical experience has proved the beneficial effect of *p*-aminosalicylic acid (PAS). Feldman, Karlson, Hinshaw & Carr (15) found impressive success in parenteral administration of PAS in experimental tuberculosis, indicating a fruitful area for further work. Eastlake & Barach (10) have reported in detail on experimental and clinical studies with the drug PAS produced a definite inhibition of tubercle bacilli growth in Dubos media. In their clinical studies they found that a dosage of 10 to 11 gm daily in courses of three weeks with one week intervals, in seven cases of advanced pulmonary tuberculosis, produced observable symptomatic improvement. Prompt reduction of cough and expectoration and decrease in fever were noted in all the patients, especially in the first week of treatment Side effects, however, such as intermittent nausea, vomiting, and diarrhea were sufficiently severe in three patients to force discontinuance of PAS treatment. The administration of PAS with other antibiotics appears to deserve investigation.

In concluding this survey of the antibiotics, notice should be taken of the highly encouraging studies of Waksman & Lechavalier (62), and Waksman, Hutchison & Katz (63), resulting in the development of neomycin. This agent, which was isolated from the soil, is a basic compound with an antibiotic spectrum quite distinct from that of streptomycin and streptothrycin. Little is known of its chemical nature, since it has not yet been obtained in crystalline form, but more detailed studies are promised for the future. It is active against numerous gram-positive and gram-negative bacteria, especially against mycobacteria, but the authors find it ineffective against fungi. It is more active than the other antibiotics against both pathogenic and saprophytic bacteria, and equally active against streptomycin-sensitive and streptomycin-resistant strains. Perhaps most important of all, it does not allow a rapid development of resistance among mycobacteria, a serious drawback in the use of streptomycin

In addition to the highly promising studies of new agents, such as neomycin, significant work lies ahead in attempts to gauge the effectiveness of various antibiotics used in conjunction with surgery and other modes of treatment It should be mentioned here that the uselessness of aureomycin in tuberculosis, the instability of myomycin for present use, and the toxicity of neomycin for clinical use in chronic disease were stressed at the 8th Streptomycin Conference held recently at Atlanta, Georgia.

## Pneumonias

*Atypical pneumonias.*—Most of the recent papers concerned with the pneumonias have dealt with the virus types, Loeffler's (33) syndrome and Q fever. Scaddings (54) reports that routine use of chest roentgen-rays in epidemics of apparently mild respiratory infections has disclosed localized consolidation of the lung in patients with none of the symptoms associated

with acute pneumonia. It is doubtful that primary atypical pneumonia is due to one etiologic agent since, except for such specific types seen in rickettsiosis and psitticosis, there is a wide variation in its character, ranging from mild respiratory catarrh to more severe infections, very often characterized by pulmonary consolidations. Psittacosis and rickettsiosis must be confirmed in instances where these entities may be suspected on epidemiologic grounds. This can be done either by isolating the agent or by demonstrating the development of specific antibodies for these two agents in the blood.

The question of how frequently these may develop in patients whose disease conforms clinically to the entity of primary atypical pneumonia has been investigated by Morgan & Finland (35). In a serologic study of 89 patients with primary atypical pneumonia, a large majority was found to develop cold hemaglutinins and *Streptococcus MG* agglutinins. Four of them developed antibodies for a virus of the psittacosis group, indicating an infection with one of these agents In the 25 patients whose serums were tested for antibodies against Q fever, only two instances were found Cold hemagglutinins were present in five additional patients who had atypical pneumonia associated with erythema multiforme exudativum, and two of these patients showed a rise in titer in complement-fixation tests for psittacosis.

*Q fever.*—The finding of specific psittacosis and Q fever antibodies make possible a definite diagnosis for these diseases, and the demonstration of cold hemagglutinins or *Streptococcus MG* agglutinins helps to confirm diagnosis based on clinical and roentgen-ray findings

Dryer (9), in summarizing the present status of Q fever, notes that infected cows, sheep, goats, the milk of any of these animals, wild animals, and a variety of ticks are the known potential sources of Q fever and, that studies have indicated that an important method of transfer of the infection to man is through the medium of contaminated air, whether this be by droplet infection or dust.

Strauss & Sulkin (59) report on the results of complement-fixing antibodies with *Coxiella burneti* antigens Tests were performed in 5,470 sera obtained from meat packing workers in Forth Worth, Texas and Austin, Minnesota, from dairy workers in the Dallas area, and other persons living in Massachusetts and Oregon. The Q fever antigen was prepared from the yolk sacs of embryonated eggs infected with a strain of American Nine Mile *C burneti* The antigen was a washed rickettsial suspension prepared by a combination of ether extraction to remove proteins and fats. Two lots of antigens were used (Q9M-5-16 and Q9M-4-26) Almost all sera reacting with *C burneti* antigens were also tested with a yolk sac antigen prepared from uninfected embryonated eggs. The evidence of Strauss & Sulkin suggests that among residents of the southwestern part of the United States there is a high incidence of complement-fixing antibodies with *C burneti*, although Q fever may occur in low incidence throughout the country

Beck, Bell, Shaw & Heubner (3), reporting on a study of Q fever epidemic

in the Los Angeles area, suggest three general hypotheses accounting for the spread of the disease in this endemic area: occupation in the dairy or livestock industries, residence in close approximation to a dairy or livestock yards, and household use of raw milk. No one of these modes would account for more than one-half of the cases, and specific epideminologic studies have been arranged for each of these hypotheses. Oliphant, Gordon, Meis & Parker (40) found, in investigating an outbreak of Q fever among laundry workers handling clothing and linens from the Rocky Mountain Laboratory, that apparently the disease can be transmitted indirectly by contact with contaminated materials.

*Pneumonitis.*—The term pneumonitis appears more often now, covering the diverse irregular consolidations of the lung due to various infections Muirhead & Haley (36) report an unusual form of pneumonitis due to rheumatic fever, their one case perhaps being typical of many unrecognized rheumatic pneumonitis. The patient presented concomitant occurrence of known healed and active rheumatic cardiac lesions and a peculiar interstitial and intra-alveolar pneumonitis, which was widespread, demonstrating a healed (proliferative) phase with extensive fibrosis and an active (exudative) phase. In addition, the partly healed arterial lesions were observed within the lungs.

In describing a delayed chemical pneumonitis which developed in beryllium workers, Hardy (25) noted that many persons exposed to identical beryllium combinations failed to develop the disease, a fact which strongly indicates that one or more additional agents may be acting. He believes the term "delayed chemical pneumonitis" inappropriate, and suggests industrial granuloma or sarcoid. He found the incidence of pneumonitis in relation to beryllium exposure over periods varying from eight months to eight years was 36 cases out of a possible 1,400 the development being gradual in all cases. The roentgen-ray findings revealed characteristic features common to the entire series, that is, a bilateral widespread involvement, but there were no striking findings on physical examination. Three cases occurred in persons not working with beryllium who lived close to the building where the fluorescent powders were being handled.

*Loeffler's syndrome.*—In reviewing Loeffler's syndrome, Ham & Zimdahl (23) refer to Loeffler's original investigation (33) together with subsequent studies. They agree that the eosinophilia can not be considered either as an expression of an anaphylactic process or the result of parasitic infection. Likewise discarded are the assumptions that the lung changes are due to emboli, localized bronchial asthma, or atelectasis. The infiltrations are differentiated from those due to early tuberculosis or pneumonia. They emphasized that repeated roentgenograms are necessary to make a diagnosis. Loeffler emphasized five characteristics of the syndrome: infiltrations show by roentgenogram, fleeting and changing character, eosinophilia, mild degree of illness, and short duration. The authors cite three recently observed cases all characterized by pulmonary infiltrations and blood eosinophilia. They emphasize that search or the etiological agent is important in every case. There may be a specific allergen to which the patient is sensit

may be a parasitic infestation Periarteritis nodosa, Hodgkin's disease, and eosinophilic leukemia must all be considered in the differential diagnosis, but can be usually ruled out by the clinical course

### Tuberculosis

Among the large number of reports on the treatment of tuberculosis, the most impressive have been those dealing with the use of antibiotics under numerous and varied conditions. Preoperative treatment of patients with the various antibiotics has resulted in a larger number of cases made suitable for surgery, while the postoperative use of streptomycin in particular has reduced the mortality considerably.

Two reports on pulmonary resection out of many may be cited here, namely, those of Bailey, Glover & O'Neill (1) and of Gale, Dickie & Curreri (18). The former, reporting on 200 consecutive lung resections corroborate the experience of Glover, Clagett & Hinshaw (19) in the use of streptomycin. Out of the entire group of specific complications commonly seen after resection which had occurred 49 times in the non-streptomycin (actually, the pre-streptomycin) series, only 10 appeared in the series of streptomycin-treated cases. Whereas these complications caused 17 of 27 deaths (63 per cent) in the first series, they caused only 2 of the 16 in the second, both of which occurred in cases which would not have been considered operable at the time the first series was in progress (mixed tuberculous empyema with bronchopleural fistula due to acute cavitary rupture). The authors believe in the efficacy of streptomycin therapy in reducing the postoperative incidence of tuberculous empyema except in cases where a clinical bronchopleural fistula develops In 23 cases where operative rupture of a caseous area led to gross contamination in the pleural space, tuberculous empyema resulted in 13 instances (58 per cent) It was found, on the other hand, that except in cases where a previous course of streptomycin therapy had not rendered the patient's bacteria streptomycin-fast, a definite suppression of the tuberculous process was produced during the preoperative therapy.

Gale, Dickie & Curreri (18), reporting on 80 cases of pulmonary resection unsuitable for usual collapse procedures, found streptomycin most valuable in cases with acute ulcerative bronchitis, where in many instances resection would have been dangerous before streptomycin was available. The drug was given in daily doses of 1.0 gm. with frequent instillations into the pleural cavity following pneumonectomy to prevent tuberculous empyema. At the time of the report, January, 1949, 67 cases of the series (84 per cent) were noninfectious, 8 (10 per cent) were still discharging tubercle bacilli, and 5 (6 per cent) had died, 2 deaths being operative.

A study of the remote results of all forms of collapse therapy in pulmonary tuberculosis is reported by Livingstone (32) of the Lenham Sanatorium (county of Kent, England) From his year by year summary of fatality rates, certain significant figures may be noted.

| | |
|---|---|
| Of 630 patients, within 1 year | 4.3 per cent had died |
| Of 616 patients, within 5 years | 30 8 per cent had died. |
| Of 415 patients, within 10 years | 57 9 per cent had died. |

When treatment of these patients resulted in sputum conversion, the death rate was as follows:

| | |
|---|---|
| Of 395 patients, within 1 year | 0.5 per cent had died. |
| Of 388 patients, within 5 years | 14 4 per cent had died. |
| Of 268 patients, within 10 years | 32 8 per cent had died. |

Whereas, when treatment did not result in sputum conversion, the death rate increased sharply:

| | |
|---|---|
| Of 235 patients, within 1 year | 10.6 per cent had died |
| Of 228 patients, within 5 years | 58 8 per cent had died. |
| Of 183 patients, within 10 years | 94 5 per cent had died. |

Notwithstanding positive sputum, some patients may continue to live a long time. However, these figures do emphasize that sputum conversion should be the important criterion of the value of any specific treatment.

## BCG Vaccine

There appears to be a narrower divergence of opinion as to the value of BCG (Bacillus Calmette-Guerin) vaccine although its effectiveness has not been conclusively established with sufficient numbers of properly controlled experiments. Reports of long term studies suggest, however, that we are approaching closer to a solution of the problem. As the editors of *Tubercle* (11) point out, there has been no evidence of any appreciable harm done by BCG while we are constantly confronted with results which demonstrate its value Rosenthal, Leslie & Loewinsohn (51) claim to have made the longest continuous experiment in the United States (13 years). Reporting on two of their studies in Chicago, they point out that among 2,831 newborn infants, when tuberculosis was present in the household and where isolation was practiced in controls and vaccinated alike, there were two cases with no deaths in the BCG group, against five cases with four deaths in the control group

On the basis of her experience in a Dublin hospital over an 18-year period with 420 unvaccinated tuberculous children under five years of age, Price (47) asserts the need for BCG vaccination among exposed infants. Of these, among 60 infants vaccinated with BCG and returned to tuberculous homes, there were no deaths from tuberculosis during the ensuing ten years, although one child did develop a calcified primary complex Ferguson & Simes (16) made a study of BCG vaccination in a highly infectious environment, that of the Plains Indians of Saskatchewan. In the group studied, 306 infants were registered as vaccinated and 303 as controls. The percentage of manifest tuberculosis was in a ratio of 1:4 85 comparing the vaccinated with the controls, and the percentage of tuberculosis deaths were in a ratio of 1:45 These authors found a more serious and generalized type of diseases among the control group, and in no case was there any recurrence of BCG virulence in the host.

The foregoing studies, among many others, indicate that BCG is probably the best answer to the problem of the infant born of tuberculous parents or

returning to a generally infectious environment. The reports of long term studies, appearing more and more frequently, make the good results of BCG vaccination increasingly convincing.

THORACIC SURGERY

Thoracic surgery is making brilliant strides in attacking diseases once considered inoperable. For example, experience in the war with pulmonary decortication in treating fibrosed traumatic hemothorax has prompted interest in adopting this procedure to the problem of the postpneumothorax nonexpandable lung. Mulvihill & Klopstock (37) describe their technique

portion leaving this tissue attached to the lung. Previous to this operation the unexpandable lung was a serious problem in thoracic surgery.

Successful pneumonectomies for carcinoma of the lung have become more numerous; early diagnosis by sputum studies, better roentgen-ray facilities, and awareness of the possibility of carcinoma all have contributed to the lower operative mortality.

Recognizing the occasional difficulty of clearly mapping lung segments during lobectomies, Rubenstein, O'Neill & Glover (52) have developed a valuable yet simple method whereby the surgeon may localize exactly the various segments of the lung to be resected. This is done by injecting methylene blue solution into the cut bronchus of the segment which then stands out clearly, enabling the surgeon to accomplish resection with the minimal sacrifice of normal lung tissue.

The development of the use of antibiotics in conjunction with thoracic surgery is an important recent development discussed elsewhere in this review. The use of antibiotics in conjunction with other methods of treatment appears as the richest field of present and future investigation.

Recent improvements in the technique of cytological studies of bronchial smears or of sputum have made earlier diagnosis of carcinoma possible. Watson, Cromwell, Craver and Papanicolaou (61) report the results of a five-year study. In their overall group of 1,200 cases, they falsely diagnosed cancer four times; in the later series of 400 cases, there were none of these "false positives." In the latter series there were 236 cases of proven bronchogenic carcinoma; 60 per cent of these proven cases were diagnosable on the basis of cytologic studies.

The method of sputum study for carcinoma cells is characterized by its simplicity: material collected after coughing is fixed immediately in 70 per cent alcohol. Smears are made and fixed in alcohol-ether, are stained first in hematoxylin and then in OG6 and EA65. A good nuclear staining is essential (The two counter stains used, OG6 and EA65, are fairly transparent and give a good differentiation of basophilic and acidophilic cells) Although this method has several disadvantages (for example, it does not show the

grade of malignancy of the cells, nor their type and origin), it is simple and inexpensive. It would appear to be useful for large-scale screening, and the authors claim it to be of unique value in following up operative procedure results and the progress of radiation or mustard gas therapy. Other detailed studies by Farber *et al.* (13) as yet unpublished, emphasize the value of cytologic study in the diagnosis of lung tumors.

Reporting a six-year study of carcinoma of the lung, Humphries (28a) presents some interesting figures. Operations were performed in 42 cases of a total of 125, resection being completed in 29. Nine died during the post-operative period; three are alive three and four years after operations. The remainder survived an average of 16 months after operation, as contrasted with an average duration of life after diagnosis in the nonoperable group of two months.

The question of whether bronchial adenoma may become malignant continues to the subject of considerable controversy. Goldman (20) asserts that from his observation, treatment by lobectomy and pneumonectomy has given approximately 100 per cent of the five year cures. The recurrence rate will have to be established by observation over several decades. "The malignant nature of malignant adenoma," says Goldman, "is not so malignant, nor is its benign course so benign."

Among other techniques in diagnosis, the reliability of the Kveim reaction in sarcoidosis continues to be in dispute. Haxthausen (26) discusses the test, and points out the fact that an antigen prepared from tubercle bacilli will sometimes produce a similar reaction to that of a suspension of sarcoid granulation tissue, thus casting some doubt on the specificity of the reaction. Pautrier (43) dismisses the theory that sarcoidosis is of tuberculous origin, nor does he find much support for the theory of an indeterminate virus as the cause, citing the doubts of investigators as to the reliability of the Kveim reaction. He concludes that the etiology remains unsettled.

## Pneumonoconioses

Hamlin (24) discusses the pneumonoconioses, noting that pulmonary diseases caused by fungus infections may be far more generally prevalent than has been supposed. He cautions medical examiners that even when roentgenologic evidence shows pulmonary alteration, it should be made certain that the occupation in a dusty industry offers adequate exposure to particles capable of causing actual damage Very few particles larger than 10 microns ever reach the alveoli, even though the diameter of an alveolus is some 250 microns. There is no conclusive evidence that silicates other than asbestos cause real pulmonary fibrosis, although pulmonary changes due, probably, to small amounts of free silica existing as impurities have been reported. Discussing the treatment of advanced silicosis, Berry (4) discounts the use of hydrated alumina, suggesting that investigators have failed to make sufficient note of the psychological aspects of this form of treatment.

## Diagnostic Techniques

Notable contributions in techniques for the measurement of lung function have considerably lessened difficulties of diagnosis. Dripps (8) describes one recently developed device which can conceivably find wide application in chest services. This is the oximeter, which, when placed on a patient's ear will record the degree of saturation of the hemoglobin by means of a photoelectric cell. As the hemoglobin becomes increasingly saturated and therefore redder in color, more light is transmitted to the photoelectric cell, thereby increasing its output of electrical current. Any delay in this response of the oximeter indicates either a slow circulation through the lungs or the presence of rather uniform and widespread pulmonary lesions, such as bilateral pulmonary edema, emphysema, or fibrosis.

Dripps (8) also reports on an instrument for lung volume measurement. If the initial proportion of nitrogen eliminated is measured, the total lung volume can be calculated; recently an apparatus for the continuous determination of the nitrogen content has been developed. This instrument contains an evacuated tube into which is passed the gas which is to be studied and through which is passed a 2,000-volt current. In the presence of nitrogen, a characteristic color is produced which increases in intensity as the nitrogen concentration increases

In a recent article Ornstein (41) describes a more accurate method of measurement and evaluation of lung function developed in conjunction with Herman, Friedman & Friedlander (64). A rebreathing bag is filled with 1,000 cc of air, and the patient, at the end of a rest period of 30 min. with the mouthpiece fixed into place and his nose clamped with a noseclip, is made to ascend and descend from an eight-inch step 30 times in a one-minute period He rebreathes from the bag for 20 sec., and the gas content of the bag is analyzed for oxygen by means of a Haldane-Boothby-Sandiford gas analyzer In cases where evaluation of pulmonary function is required, physicians will welcome this more accurate method of determination.

## Pathological Physiology

Sante (53) discusses from an anatomical standpoint the structural safeguards of the thin capillaries for withstanding pressure from the distended alveoli. The alveolar walls are guarded from overexpansion by elastic fibres, whereas the capillaries have only a fine fibrous stroma. The increase in blood volume in the lung during deep inspiration is explained by the fact that the capillaries, thus guarded from pressure by overdistension of the alveoli are themselves subject to change in intrathoracic pressure. Therefore, the development of a negative pressure in the thorax during inspiration produces greater vascularity as well as greater engorgement of the capillaries in contact with the alveolar membrane, both desirable effects in aeration of blood. On expiration, pressure of distended alveoli on the capillaries squeezes out the excess blood, thus producing the pumplike action which is a potent factor in aiding pulmonary circulation.

Particularly interesting is Sante's discussion (53) of lymphatic structure Describing the respiratory bronchiole, he notes the lack of lymphatic structure peripheral to the alveolar ducts, indicating that the alveolar membrane would have to become extremely swollen and edematous and fluid would have to exude into the alveoli before it would be subject to absorption by the lymphatics. There is an immediate increase in lymph flow from the right thoracic duct upon obstruction of the pulmonary vein, indicating immediate transudation through the capillaries into the tissues and then into the lymphatics.

The lesser circulation of the lung has had the attention of workers in the field of roentgenology. Good & Dry (21) discuss the signs of pulmonary hypertension which can be disclosed under roentgen-ray analysis, enlargement of the pulmonary arteries and of the overflow tract of the right ventricle (conus), and enlargement of the right side of the heart. In a typical case the roentgenologist will see the convex left border of the heart possibly with some enlargement of the cardiac silhouette. The aortic knob may be less prominent than usual because of rotation of the heart on its vertical axis, and the hilar vessels may be dilated.

The various conditions which cause pulmonary hypertension are classified by the authors into the following groups. (*a*) obstruction to the lesser circulation beyond the pulmonary circuit, (*b*) obstruction within the pulmonary system, (*c*) abnormal shunts of the blood from the arterial side into the pulmonary circulation, and (*d*) kyphoscoliosis Diagnosis of pulmonary hypertension is often possible, say the authors, before roentgenologic signs of pulmonary infarction and pleural reaction appear

Chapman, Gugel & Wheeler (6), reporting on an experimental study of infarction, conclude that more than embolism alone is necessary to produce infarction, although they do mention the work by Steinberg & Mundy (58), who produced occasional infarcts with lead shot. They note that embolism alone does not result in infarction of the normal lung because the bronchial arteries anastomose with branches of the pulmonary arteries; clinical and autopsy observation suggested that pulmonary congestion, edema, or both were prerequisites for infarction to follow an embolus.

In the majority of cases of pulmonary tuberculosis, emphysematous changes are localized in the area and immediate vicinity of the tuberculous lesion. Guggenheim (22), in a study of pulmonary emphysema, classified these changes· (*a*) intrafocal emphysema, (*b*) perifocal emphysema, (*c*) emphysematous bullae and blebs, (*d*) interstitial emphysema, and (*e*) diffuse (compensatory) emphysema In only a small minority of cases can the changes be explained on a compensatory basis. Localized emphysema, whether intrafocal or perifocal, as well as bullae and blebs, are due to bronchial changes. Obstruction of bronchi and bronchioles is caused by exudate, necrotic material, endobronchial tuberculous lesions, compression, torsion, and stretching. In hypertrophic emphysema, bronchial changes are of primary importance, while in atrophic emphysema vascular changes are of greater significance.

Emphysema occurs during all stages of pulmonary tuberculosis. It is of characteristic appearance in many cases of hematogenous tuberculosis.

Mokry (34), discussing the development of endopleural bullae, described a case, a 16-year old patient with atypical adhesions in which the thoracoscope encountered a large endopleural bulla in the second intercostal space in the mammary line. Histological examination of the wall of the bulla showed fibrinous connective tissue with fissurelike cavities lined with endothelium-like epithelium, obviously residues of an obliterated pleural cavity. Pleural bullae are not infrequently found during endoscopy.

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# PHYSICAL AGENTS AND TRAUMA

## SHOCK AND BURNS[1]

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The late war spurred on many clinicians and experimental physiologists to research on the mechanism and management of shock and observations on better methods for the treatment of the burned patient. This enthusiasm has now largely died This is unfortunate because during peacetime as well as war, death or disability from shock or burns is common. There are many unsolved problems in these fields, and it is to be hoped that attempts at their solution will not await another armed conflict.

*Estimation of blood volume*—No appraisal of current investigations and observations on shock or burns could be complete without an analysis of continuing efforts to increase the reliability of methods for the estimation of plasma and red cell volume. The definite establishment of the concept that traumatic shock is initiated by severe blood loss was made possible during the past war only by application of methods for plasma volume estimation to experimental and clinical subjects. Since then, there has been increasing interest in the actual measurement of red cell volume by tagging methods, rather than its estimation from hematocrit-plasma dye dilution figures.

In 1947 Cruickshank & Whitfield (1) reported that a variable portion of the initially injected T1824 dye was phagocytized by the reticuloendothelial system, thereby blocking that system so that of the second injection of the dye would be available for dilution. They felt that plasma volume determinations based on the single injection dilution technique would, therefore, be subject to a possible error of 20 to 30 per cent. Campbell, Sokalchuk & Penman (2) have conducted experiments on man, making two determinations of plasma volume on resting normal adults with a 30-minute interval between the two determinations. If the effect described by Cruickshank & Whitfield (1) were present, the first determination should be appreciably higher than the second. They used single 10-minute samples for calculations of plasma volume In none of the six experiments did they find a disagreement of more than 2 1 per cent, and the variation was usually close to 1 per cent This and other work would indicate that the Gregersen technique is valid for plasma volume estimation in resting man, but the reviewer would warn against the use of single 10-minute sampling in plasma volume estimations. This is emphasized also by Rossiter (3) who found a negative correlation between the slope of the disappearance curve and the plasma albumin level during the

[1] This review covers the period from approximately January, 1948 to July, 1949.

estimation of plasma volume on prisoners of war who had been held in captivity for 3½ years.

Further attempts have been made to compare blood volume by red cell tagging methods and dye plasma methods. Courtice & Gunton (4) have reinvestigated this problem, tagging the red cell with carbon monoxide, using an hematocrit correction factor of 0.96 in the plasma dye method. In studies on 16 normal males, the carbon monoxide blood volume: dye blood volume mean ratio was 1.03 In a separate study on rabbits (5), they found a ratio of 1.02. These studies confirm the earlier reports of Root, Roughton & Gregersen (6).

Moore, Shaddle & Lawson (7) tagged the red cell with methemoglobin by letting blood stand for 10 to 15 min. with sodium nitrite, injecting such tagged cells and comparing red cell volumes thus obtained with calculated red cell volume from the plasma volume determined with dye T1824 after multiplying by the hematocrit. By this method, in the dog, the red cell volume as estimated by dye-hematocrit is 14 to 22 per cent above that determined by the methemoglobin technique. Therefore, the values are similar to those obtained with radioactive iron. This may prove to be a simple, useful technique for determining red cell volumes.

Barnes, Loutit & Reeve (8) have utilized the Ashby technique (the determination of the number of inagglutinable erythrocytes in the subject) for precise estimation of red cell volume, and show that on the average, the red cell volume calculated from plasma volume and hematocrit corrected for trapped plasma was 13 per cent greater than by the Ashby technique. They believe the difference is due to an overestimate by the dye method and not to an underestimate by the Ashby technique. In a separate paper (9), the same authors discuss the matter of dye loss from the circulation when T1824 is used, and conclude that the changes in plasma dye concentration during the first few minutes after dye injection is due to mixing and not to dye loss. They further conclude that the chief cause of the overestimate of the red cell volume by the dye hematocrit method is unequal distribution of the plasma and red cells through the blood.

Ever since Hevesy's (10) demonstration that the red cell can be tagged with radioactive phosphorus and such tagged cells used for estimation of red cell volume, efforts have been made to simplify this technique for wider application to clinical problems. Reeve & Veall (11) utilized especially constructed Geiger-Muller counting tubes which take liquid samples so that drying of the samples need not be carried out for the estimation of the radioactivity of the sample of blood Following injections of washed $P^{32}$ labelled red cells, $P^{32}$ is lost very slowly from the circulation [confirming Nylin (12)]. In a series of 13 normal subjects, utilizing this simplified liquid counting technique, if proper corrections are made for the trapped plasma in the T1824 hematocrit, the mean ratio of washed $P^{32}$ red blood cell volume divided by T1824 hematocrit red blood cell volume is 0.87. This ratio is considerably lower than that obtained by carbon monoxide tagging methods.

Using a correction factor of 0.915, and tagging red blood cells with $P^{32}$, Mayerson, Lyons *et al*, (13) in studies on 10 normal and 35 hospitalized persons found this ratio to be 0.96 for 10 normal persons, 1.03 for 12 male patients, and 0.87 for 8 female patients. The average for all subjects was 0.96. In a similar study carried out in the reviewer's laboratory (14), observations on 42 hospitalized subjects with the same correction factor used by Reeve (i e, 0.915), the mean ratio was found to be 0.87 [same as Reeve *et al.* (11)].

Reeve has published a splendid review (15) of the methods of estimating plasma and red cell volume, in which he critically analyzes the varied results obtained with all methods currently in use. Reeve's review placed special emphasis on the more recently developed red cell tagging methods. This reviewer knows of no better clear-cut analysis of these various methods and the reader is advised to consult this paper for the best available recent information on this subject.

The reviewer would point out that in most of the published work on tagged red cells, the subjects have been in a normal state. No critical analysis has yet been made of the reliability of these methods in patients in the shock state because of trauma or burns.

It is gratifying to note the continued application of blood volume techniques to the study of the hospitalized patient. In this manner, physiologic insight is gained and improved methods of treatment will result. Lyon and co-workers (16) have studied fluid shifts in the postoperative patient. In those patients allowed fluids by mouth or given parenterally, there was noted a 10 to 15 per cent increase in fluid space (thiocyanate), and a 15 per cent increase in plasma volume, with generally a decline in red cell volume during the first days following operation. In other words, there was no tendency for the depleted red cell volume to be restored from so-called available red cell stores If the blood lost during an operation (generally underestimated), was not replaced, anemia resulted. Further, they found by blood volume measurements a second more insidious blood loss after operation. As indicated in earlier studies, there is a mechanism able to restore depleted plasma volume, but none to restore depleted red blood cell volume. They rightly suggest that a decrease in the hematocrit on the third or fourth postoperative day indicates the need for whole blood transfusions.

Pheron & Wilson (17) estimated the red blood cell and plasma volumes in groups of patients with severe peritonitis. In those who recovered, there was no early reduction of blood volume, no matter how intense and diffuse the peritoneal irritation. After eight or more hours, the reduction in plasma volume was 20 to 30 per cent, with only a small reduction in red blood cell volume. With intravenous infusions, the plasma volume quickly rose to normal levels In the fatal cases, there was an early and larger reduction in plasma volume. The blood volume either did not rise with intravenous infussion or a further but not always large fall occurred just before death. In most cases, the fall in circulating plasma albumin was somewhat greater than that

of globulin. Also, globulin readily re-entered the circulation, but there was an albumin deficit as long as two months after illness began.

Beling & Bosch (18) illustrate how simply one can carry out determinations of plasma and red blood cell volume with sufficient accuracy in hospitalized patients. McLennan & Thuoin (19) observed a 40 per cent increase in plasma volume in 20 normal pregnant women at term; the red blood cell volume showed a smaller increase. This paper and the labored discussion by Sheehan (20) on the cause of obstetrical shock indicate the need for further observations on plasma and red blood cell volume in the obstetrical patient; in this group, red blood cell tagging by radioactive phosphorus should give valuable information

*Oligemic shock.*—In an important paper on the historical aspects of traumatic shock, Phemister (21) calls attention to the contribution of animal experimentation to our understanding of the cause and proper therapy of surgical and traumatic shock. He correctly evaluates the debt all clinicians and patients owe to the demonstration that blood and plasma loss is the outstanding cause of shock and that nervous impulses are of minor importance. This one fact has led to the enormous increase in the use of blood, plasma, and plasma substitutes in the prevention and management of clinical shock. In the continuing battle of the antivivisectionists against animal experimentation, the clinician and patient who have benefited by the increased knowledge of shock should acknowledge the importance of animal studies.

Unfortunately, the observations made by Grant and his co-workers (22) on shock seen in the British army during the Italian campaign are not yet generally available. These are referred to by Stammers (23). Grant and his co-workers divided clinical shock patients into two categories (*a*) cold hypotension, and (*b*) warm hypotension In (*a*) the combination of blood pressure under 100, and a pulse rate of 100 or more was associated with pallor of the face and coldness of the extremities. Seen in a recently injured patient, this combination is a sure sign that he has suffered a 30 per cent blood loss and indicates the need for a transfusion. This syndrome is met with before, during and after operation. The syndrome (*b*) is seen in patients previously transfused and more often during and after, than before operation. One finds that a low blood pressure and a fast pulse are usually associated with fair facial color and warm extremities; this syndrome usually indicates that the blood volume has not yet been restored to normal and indicates the need for further transfusion In the reviewer's experience, shock may be present in patients with warm or cold extremities (24) irrespective of transfusion. It is well to continue blood replacement until blood pressure is above 100, and the extremities become warm. In general, however, our observations agree quite well with those of Grant and his co-workers.

Venning & Browne (25) report on the excretion of glycogenic corticoids following acute trauma, such as surgical operations, burns, fractures, wounds and infections in both the previously healthy individual and the chronically

ill debilitated person. The results are as follows: when a healthy, well-nourished individual is subjected to acute trauma, there is an immediate and rapid increase in the ouptut of glycogenic corticoids, reaching a maximum in three to four days. This elevated output is maintained for a varying period of time. In most cases, the corticoid excretion has returned to a normal level by the end of the third week. Usually the values lie between 200 and 300 units. There is usually an immediate rise in 17-ketosteroid excretion, but this increase is not always maintained. The changing levels of 17-ketosteroids and corticoid excretion do not parallel one another. In the chronically ill person suffering from malnutrition, the response is markedly different from that seen in the healthy individual Following acute trauma, there may be no increase in glycogenic corticoids or else the increase is maintained for only a few days, reaching normal levels again by the end of the first week. Thus these studies indicate the same trend in corticoid excretion as was found earlier in studies on nitrogen metabolism, with a similar difference in the response of the healthy and the malnourished individual.

*Shock in bleeding peptic ulcer.*—Probably in no branch of medicine or surgery has the application of blood replacement methods been so effective in the management of shock as in the patient with bleeding peptic ulcer. It may be said that this knowledge is altering the method of treatment of these patients.

Stewart *et al.* (26) gave massive transfusions but performed immediate gastric resection in the therapy of patients with grossly bleeding peptic ulcer. In their series, 33 were operated on, and 21 without operation served as controls. A subtotal gastric resection of antecolic Hofmeister type with removal of 80 per cent of the stomach was performed. They gave an average of 3,600 cc. blood In the operated group the mortality was 15 per cent, the unoperated, 29 per cent They believe that, although the reported group is small, they are safe in concluding that more lives are being saved by early adequate blood replacement and gastric resection than by the nonsurgical plan of management. One important observation in this study concerns the fate of administered hemoglobin. Despite the administration of blood to exceed by 25 per cent that estimated by theoretically required values (after control of hemorrhage), at the end of 24 hr, 22 per cent of the administered hemoglobin had left the circulation and at the end of 15 days, 35 per cent was missing This study indicates three things. too little blood is ordinarily given to the patient with bleeding peptic ulcer, secondly, the serious need for studies on the method of utilization and fate of hemoglobin in the transfused patient; and thirdly, with proper blood therapy, this group of patients can usually be operated on safely

Hoerr, Dunphy & Gray (27) have attempted to work out a routine to differentiate between those patients with a bleeding ulcer who need operation and those patients who can be treated conservatively. If shock develops despite transfusions of 500 cc. whole blood every 8 hr., it is considered that

the rate of bleeding makes surgical operation imperative. These workers recognize that age is a factor and that old age (over 50 years) is a warning that there is a greater danger of exsanguinating hemorrhage, and that if it develops, surgery is usually necessary.

Holman (28) recounts the experience of the surgical group at the New York Hospital from 1940 to 1946 in hadling this problem. There, early operation (gastrectomy) is done on all patients who (*a*) fail to improve in from 24 to 48 hours on a strict medical regime, and (*b*) those who suffered the first hemorrhage while under a strict medical regimen for hitherto uncomplicated ulcer. From 1940 to 1946, with such a plan, 206 patients were operated on and mortality was reduced to 5 per cent. Ninety-six patients were discharged from the hospital without operation.

Conversely, two well-documented papers were published in 1949 which indicate that with adequate blood replacement in the management of shock, surgical operation for bleeding peptic ulcer may prove unnecessary. Costello (29) analyzed a series of 300 cases of massive hematemesis in the St. Louis Hospital, and found that the most important single factor in minimizing death has been blood replacement, to the extent of 3 to 4 l. of blood during the first 24 hr. Such nonsurgical management in 73 patients resulted in a mortality of 4 per cent (Reviewer's note: In this paper there is one error, that of advocating the use of the copper sulphate method for blood specific gravity for the estimation of blood loss. Unless hemodilution takes place, and it may not, blood loss may not be suspected). Fraser & West (30), in a study of 177 patients with bleeding peptic ulcer, found that following operation upon 12 patients there were four deaths (33 per cent), while with conservative management of 65 patients there were 7 deaths (4 2 per cent). The operated group is obviously too small for comparison

Seavers & Price (31) have shown that transfusion prior to blood loss does not necessarily give added protection to a patient who may lose blood during operation, if the blood volume (plasma and red cell) is normal before transfusion

*Plasma substitutes.*—During the past year little information on newer plasma substitutes has appeared in the literature except in the case of the product Dextran. This is a plasma substitute produced by the growth of the microorganism, *Leuconostoc mesenteroides*, in a substrate of sucrose and phosphate. By enzymatic action, this organism produces Dextran from sucrose. It can be degraded by acid hydrolysis, and with proper precipitation methods material of known range of molecular sizes can be produced. It is being supplied by Swedish and English pharmaceutical firms in 6 per cent concentration in saline solution, so that the osmotic pressure is about one and one half to two times that of plasma

Extensive studies have been made in Sweden on this substance, and from 1943 to 1947 several reports appeared in the Swedish literature (32). In 1949, Thorsen (33) summarized the Scandinavian experience with this plasma

substitute, stating that 20,000 units have been given to 5,000 patients. In a few cases, as much as 4 l. were given and in one case, 10 l. were used. So far as they can tell, Dextran is nontoxic and does no injury to tissues. It has found good use in the prevention and treatment of shock. In Sweden today it has replaced plasma for emergency use. Rosenquist (34) has used Dextran effectively at the St. Gorains Hospital in Stockholm for the treatment of burn shock.

Bull *et al.* (35) report on the British experience with Dextran. They have developed an antiserum to this substance which permits them to estimate its presence in tissues with a sensitivity of 1:1,000,000. It appears to be nontoxic, 10 to 22 cc. per kg. per day has been given for seven days to rabbits and histologic examination of liver, kidney, spleen, cardiac muscle, thyroid, and suprarenals up to 90 days after infusion has revealed no abnormalities. Dextran can be identified in tissues by their immunological tests for as long as 56 days following infusion. Dextran was given to 29 patients undergoing operation and no pyrexia or anaplyhactic reactions were noted. They have given Dextran to four seriously burned patients with good correction of hemoconcentration Bull and his co-workers draw one important inference from their observations, i e, that no one knows how Dextran is dealt with by the body; there is no evidence to support the view that Dextran is metabolized as glucose.

Turner *et al.* (36) gave Dextran to 30 patients and noted reactions of an anaphylactoid or anaphylactic nature in 10 of these subjects. They noted regularly hemodilution and an increase in plasma volume when the substance was infused. All patients receiving Dextran had a marked increase in sedimentation rate commonly seen after infusion of macromolecular substances. In six dogs receiving large quantitites of Dextran after bleeding, histological studies showed focal degenerative lesions in the liver and kidneys, but minimal reticuloendothelial hyperplasia of the spleen. These were not observed in the studies of Grönwall, Thorsen, Ingelman, or Bull and his co-workers, and may indicate that this latter group were working with a Dextran solution containing excessively large molecules. Nevertheless, the reviewer believes a great deal more careful work and observations are necessary before Dextran can be finally endorsed as a safe and satisfactory plasma substitute. It appears to be a promising and effective plasma substitute, especially for large scale emergency use, and it is to be hoped that adequate investigations on it will proceed without delay.

*Intra-arterial transfusions.*—Following the suggestions of Colonel Sam Seeley of the possible usefulness of intra-arterial blood transfusion, rather than intravenous in the treatment of shock, several surgical groups have investigated the method. Robertson, Trincher & Dennis (37) bled dogs and maintained the blood pressure at shock levels for 30 to 75 min. In the intravenous group, blood was infused at rates of 10 to 25 cc per min and in the arterial group, at a rate of about 100 cc. per min. Both groups had the same

survival rates, but they believed recovery from shock was much more rapid in the intra-arterial group. This was to be expected, because the rates of administration were so much more rapid in that group (100 cc. per min. as against 10 to 25 cc. per min.). They have used intra-arterial infusion in shocked patients with dramatic results. Porter, Sanders, & Lockwood (38), using a slightly different apparatus, have given blood by the intra-arterial route at rates up to 500 cc. per 3 min. in six patients in surgical shock. One patient described illustrates the disadvantage of sacrificing the radial artery for arterial infusion. Gangrene of the hand developed in this patient. In the discussion of this paper, Jenkins advises the use of a Gelfoam sponge to control hemorrhage from the artery when the needle is withdrawn to obviate the necessity of ligation of the artery employed for the infusion. Page (39) retains his enthusiasm for the intra-arterial method of transfusion after several years extensive experience with its use in experimental and clinical shock.

Fatal air embolism continues to be reported following intravenous blood transfusion (40, 41). This danger is always present with the use of ordinary types of transfusion equipment. That this may happen in any intra-arterial infusion should be apparent, because here air pressure is used to drive the blood into the arterial system.

*Experimental studies in shock.*—Admirable is the continuation of studies which have as their objective the development of a standard shock preparation. With such a preparation, Allison *et al* (42) have demonstrated that the most striking difference between dogs permanently resuscitated and those dying after volume replacement is the much higher volume of urine flow and a much higher rate of phosphate excretion in the dogs which survived In animals treated only with saline, all died, there was a higher rate of survival of the whole blood transfused group (8 out of 21) than when plasma alone was infused (only 3 out of 16). Glucose and sodium bicarbonate given as adjuvants to whole blood infusions were not effective in increasing survival rates from deep shock (43).

The group under Page (44) have made the most serious and painstaking effort to develop a standard shock preparation. Their studies indicate marked variation in survival of such a standard preparation according to the season of the year when the study was conducted. To the reviewer, this indicates the growing need for a purer strain of experimental animal for studies on shock and burns, where survival rates are in question. Fine and co-workers continue to report their excellent studies on the role of the liver in shock (45). If the rise in blood amino acid nitrogen consequent to shock is referable to failure of deaminization by a damaged liver, administration of amino acids during shock should result in abnormal persistence of the amino acid in the circulation. Administration of a series of amino acids during shock in doses of 100 to 200 mg. per kg. was carried out, and the results indicate no serious disturbance of deaminization by the damaged liver The rise of blood

amino acid levels during the oligemic phase of shock is due rather to deficient liver blood flow.

Attention is called to the possible active role of smooth muscle sphincters of the hepatic veins in obstructing flow in the portal vein during the shock state by the observations of Macgraith, Andrews, & Wenyon (46), who produced centrilobular lesions of the liver by sensitizing portions of the liver to foreign protein. In some dogs after the first injection, small amounts of horse serum were injected into a segment of the portal vein, and the portion of liver supplied by that segment became congested. The authors point out that these results are concerned only with anaphylactic shock but they may have more general significance.

Wang & Overman summarize (47) the experience in Gregersen's laboratory of attempts to assay the role of neurogenic factors in experimental trauma. They believe that they possess evidence to prove that there is an afferent nervous factor second in importance only to blood loss as an essential causative mechanism in experimental traumatic shock. Certainly an open mind is necessary to evaluate these studies, but the reviewer is impressed with the remark of Phemister (21) "that animal experimentation has served to detract from rather than to augment the nervous theory of shock." In the reviewer's experience with approximately 500 clinical shock patients, the nervous theory has seldom, if ever, had to be invoked to explain the cause of shock in a given patient.

Wiggers and his group (48) have attempted to determine the effect of blocking the sympathetic nervous system in preventing or slowing up the development of irreversible shock in dogs in whom shock was produced by an initial severe hemorrhage They report the results in two series. In the first series Dibenamine was given 30 min before hemorrhage. It is obvious that the bleeding volume was much less in the Dibenamine treated dogs than in the controls. In the first series, there was a much poorer survival from shock in the Dibenamine treated dogs than in the controls (Dibenamine 25 per cent survival, controls 41.7 per cent). In a second series, Dibenamine was given 20 hr. before hemorrhage, and shock was slightly more severe. In Dibenamine treated dogs, the recovery rate was 60 per cent, controls 30 per cent. They conclude that in the second series prolonged accentuation of vasoconstriction induced by severe hemorrhage was prevented by blocking of sympathetic ganglia. Frankly, the reviewer fails to see that they have adequately explained the difference of results in the two series of experiments, one which favors their view, the other contraverting it. In a similar study, Glasser & Page (44) blocked sympathetic ganglia with tetraethyl-ammonium chloride and believed they found a significantly increased survival in treated dogs.

*The effects of shock on the kidney.*—Van Slyke has summarized (49) the experiments of the Rockefeller Institute group on the effects of shock on the kidney These experiments have shown (*a*) that renal ischemia occurs during

shock, (*b*) that renal ischemia caused by temporary occlusion of renal arteries in animals is followed by renal failure, either transitory or fatal depending on the duration of the ischemia, and (*c*) that similar periods of severe shock in man are followed by similar transitory or fatal renal failure. During the ischemic phase of shock, they found almost complete extraction of *p*-aminohippurate (PAH) from the plasma, explaining this by the assumption that when renal blood flow is decreased by hemorrhage or trauma this flow is completely shut off from only part of the nephrons, while those that continue to be perfused continue to function in a normal manner. Van Slyke is inclined to believe that the shunting mechanism described by Trueta is not operative in hemorrhagic or traumatic shock in view of this high rate of PAH extraction in the early ischemic phase of shock. Van Slyke also favors the view of Lucké that the chief cause of lower nephron nephrosis following shock is renal ischemia, the deposits of hemoglobin products in the tubules being of only minor importance. This excellent paper is written in terms simple enough for the clinician to follow and understand, and contains sage advice on the clinical management of disturbed renal function following shock.

Philips & Hamilton (50) investigated the effects of 20, 60, and 120 min. of ischemia on glomerular and tubular renal function and found that when renal arterial clamps were removed, renal blood flow was quickly resumed at a nearly normal rate. When only 20 minutes of ischemia was used, proportions of PAH and creatinine extracted from the plasma was not appreciably affected, but after two hours of ischemia, they were reduced markedly, especially the amount of creatinine extracted. From their studies, they concluded that it appeared probable that the diminution in extracted fractions were due to tubular injury which decreased the tubular excretion of PAH but increased tubular reabsorption of creatinine from the glomerular filtrate. These findings support Lucké's view that postshock uremia is the result of tubular reabsorption of excretory products.

Several papers appeared in 1948 on the treatment of renal insufficiency following the shock state. The reviewer is inclined to think that of Muirhead & Hill (51) is the best for the average clinician They stress the importance of conservative therapy with restriction of fluids during the oliguric or anuric phase. Both they and Coller, Campbell & Iob (52) emphasize the danger of extreme mineral depletion that may result when copious diuresis occurs in the recovery phase.

Trials of peritoneal lavage for the treatment of acute renal failure continue (53, 54) but from the latest report of Fine's group (who have had extensive experience with the method), it is clearly evident that peritoneal irrigation is not yet suitable for routine clinical use. Muirhead & Reid (55) describe a simple artificial kidney composed of a mesh impregnated with ion exchange resins, but because these resins appear to impart toxic reactions this method is not ready for clinical trial.

Solymos (56) describes a case of ischemia of the renal cortex of the

Trueta type in a patient with anuria from eclampsia. Black & Saunders (57) attempted to demonstrate the Trueta shunt in the kidney after sciatic stimulation. They observed unequivocal changes in renal PAH clearances in only half of the animals studied. In a second series of experiments, blood from one renal vein was diverted through a plastic tube to the external jugular vein, enabling them to measure renal vein pressure and secure samples of renal vein blood. In eight cats and one rabbit they observed a renal vein flow of 10 cc or more per min., so in these experiments the fall in PAH extraction to around 60 per cent cannot be ascribed to renal ischemia. However, they could not attribute the fall to induced nerve stimulation, because it occurred equally well without it. They suggest rightly that speculation on the part played by the Trueta shunt has far outrun any serious attempt to devise means of recognizing when the shunt is in operation in man, and suggest that the following criteria should be satisfied before invoking the operation of such a shunt: (*a*) low clearances of inulin and PAH with some rise in the ratio of inulin clearance divided by the PAH clearance, (*b*) an extraction of PAH by the kidney of less than 80 per cent, and (*c*) absence of gross changes in the general circulation.

Snyder & Culbertson (58) give a very good historical résumé of the experience of the U. S. Army Medical Groups (Mediterranean) with pigment nephropathy following shock in 99 battle casualties. They conclude that the renal failure in these cases was due to renal ischemia and deposition of pigment (either myoglobin or hemoglobin) in the distal tubules.

*Books and reviews on shock.*— Page (39) presents a well balanced review of the clinical shock problem with emphasis on (*a*) the state of irreversible shock, (*b*) the fact that shock affects all tissues, not just the liver, kidney, and brain, and (*c*) the value of intra-arterial infusion in clinical shock, recognizing that in most shock patients (probably 90 per cent if seen early), intravenous infusion at moderate rates correct hypotension.

Davis (59) has written a well documented collective review of the literature on shock which is useful to those interested in animal shock research, but may not be particularly helpful to the clinician confronted with a shock patient. This is not the author's fault; the fault lies in the almost studied neglect of the shock patient in shock research. Hardin (60) has published a remarkably clear account of the clinical aspects of shock to which the reader is advised to go for a rational, easily read survey of current clinical thought on this subject.

*Thermal injury*—In general little progress has been made in the past few years in improving methods for the care of the burn patient. This despite the fact that death from burns in the United States alone is in the range of 6,000 per year and there is an enormous hospital expense involved in those many thousands (in the U. S. probably 100,000 per year) who survive.

Allen (61) discusses methods used at the Cook County Hospital for early

removal of burn slough. Dakin's solution employed with pressure dressings have been discarded, because the method is time-consuming and painful to the patient. They have tried 1 per cent pyruvic acid paste, introduced by Connor & Harvey (62), but do not like it because the dressing has proved painful. (Reviewer's note: a thorough reinvestigation of the pyruvic acid method is needed. The reviewer has personally seen good results with its use.) Allen prefers surgical excision on or about the 10th day. Following excision down to bleeding tissue and dressing, the wound is left undisturbed for three to four days when the patient is returned to the operating room and split-thickness grafts placed on the wound. In his hands, primary surgical excision has not been feasible because it is difficult to estimate correctly the depth of the burn on first inspection. (Reviewer's note: Recently, I have seen excellent results from primary surgical excision and immediate skin grafting in moderately extensive burns at the Birmingham Accident Hospital, England. Surgeon, Mr. Dallas Ross.)

Brown, Farmer & Frank (63) have applied very thin aluminum foil as a primary burn dressing, with moderate pressure, and noted early healing of partial skin thickness burns. They believe the full thickness burn areas remained free from clinical infection with this dressing but no bacteriologic studies were reported. It should be remembered that partial thickness burns heal rapidly (8 to 10 days) irrespective of what type dressing is used.

Bull, Squire & Topley (64) have experimented with a new nylon derivative film as a primary burn dressing in an attempt to find a substance which is an efficient barrier against bacteria. This dressing appears to prevent bacterial ingress from the outside dressings, does not macerate the skin, and the skin under the dressing does not become excessively moist

Brown, McDowell & Fryer (65) presents an excellent paper on the management of patients with burns following excessive exposure to x-rays used for local therapy. This paper illustrates the dangers associated with x-ray therapy and the care that must be taken in its use in the human. These authors have achieved splendid results by plastic surgery with different types of skin grafts.

Cope *et al.* (66) have made studies on the protein content of bleb fluid and plasma following extensive burns in the human. These studies indicate, but do not prove conclusively, that following thermal trauma, immediately after burning there is an increase in plasma protein concentration rather than a decrease, and that the fall in plasma protein concentration following burns might be due to intravenous therapy of saline solutions.

Keyser (67) studied nitrogen excretion following severe burning in the human, finding a negative nitrogen balance in patients unable to ingest adequate amounts of food. This has been reported many times before, but needs continuing emphasis, namely, that efforts should be made to achieve nitrogen balance by oral intake of food. In the reviewer's recent experience this can usually be done by feeding through an indwelling nasal tube.

For those interested in the care of burned children, Morrison (68) gives a good general discussion of the various effects of burns in the child, with a rather good demonstration of hematocrit findings in the very young.

Block & Tsuzuki (69) present the first detailed account of the follow-up observations being conducted on the burn victims from the atomic bomb explosions at Hiroshima and Nagasaki. They observed many cases of thickened, hypertrophic burn scars and true keloids but are inclined to believe that the increased incidence of keloids in these victims is due to severe infection and slow healing of the burns, rather than some peculiar effect unique to atomic radiation. Pearse, Payne & Hogg (70) have attempted experimentally to reproduce in pigs the type of flash burn seen following atomic bomb explosion. They believe that of the readily available substances that burn quickly (of the order of 0.1 sec.) pure magnesium powder is probably the best to use. Such flashes produced in the shaved pig burns that varied from moderate erythema to a deep burn Histologically, the flash burn from magnesium presented features not noted in the ordinary low temperature burn. The epidermal transition from burned to normal epithelium is abrupt, not gradual Healing of the flash burn is different. a superficial eschar is formed, this subsequently sequestrates and epithelium grows out freely beneath the unorganized eschar until healing is complete

Bull & Squire (71) have applied the method of probit analysis to a study of mortality in the Birmingham Accident Hospital (England) Burns Unit, reviewing 794 burn patients. They have developed a simple method which by arithmetical addition only will permit a comparison between the results of different hospital burn centers. This type of study has been long needed, and application more generally of this method should permit the surgeon to evaluate adequately various methods of burn therapy.

Colebrook and co-workers (72) have continued their painstaking efforts to control infection in the burned patient They believe that many if not most burns become infected because the air of rooms in which burn dressings are done is contaminated with pathogenic bacteria Since 1945 at the Birmingham Accident Hospital, a serious attempt has been made to eliminate air borne infection by dressing all burns in a specially designed room continuously supplied with twice filtered and warmed air at a rate of 1,000 cu. ft per min Penicillin ointment was used on the burn wound, practically no penicillin being given systemically. They have practically eliminated streptococcal infections but are still bothered by pyocyaneous, proteus, and staphylococcus contamination of the burn wound if the hospital stay is long. Colebrook's group suggest the urgent need for research on methods to eliminate pyocyaneous and staphylococcus infections, especially in the control of cross infections in the burn ward This paper has revived the controversy of local versus systemic penicillin therapy for the burn wound, a controversy that was not settled by burn research during the late war Moore, Evans & Ball (73) made an important contribution in attempting to measure the sodium require-

ments of the burn patient, employing classical chemical methods and radioactive sodium 24 in analysis of burned skin. Radioactive sodium moved rapidly into burned skin early after the burn, but not after three days, indicating at that time that the burn area had lost contact with the general circulation. In a practical sense, these studies allowed Moore and his associates to calculate the deficit of sodium in the circulation imposed by withdrawal into the burn area. In one calculation, assuming a 50 per cent burn in a 70 kg man, approximately 4½ kg. of skin would be burned, and this would impose a deficit of 35 m. eq. of sodium which could be supplied by only 450 cc. normal saline solution. Since this is roughly only 1/20 of that usually required in the first 24 hours by a seriously burned patient, it is obvious that sodium is needed for reasons other than to replace exchange in the burned skin.

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ments of the burn patient, employing classical chemical methods and radioactive sodium 24 in analysis of burned skin. Radioactive sodium moved rapidly into burned skin early after the burn, but not after three days, indicating at that time that the burn area had lost contact with the general circulation. In a practical sense, these studies allowed Moore and his associates to calculate the deficit of sodium in the circulation imposed by withdrawal into the burn area In one calculation, assuming a 50 per cent burn in a 70 kg. man, approximately 4½ kg. of skin would be burned, and this would impose a deficit of 35 m. eq. of sodium which could be supplied by only 450 cc. normal saline solution. Since this is roughly only 1/20 of that usually required in the first 24 hours by a seriously burned patient, it is obvious that sodium is needed for reasons other than to replace exchange in the burned skin.

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# ANESTHESIA

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Material included in this review was published between June 1, 1948, and June 1, 1949. Any references dated previous to this period are included only because they are important to the text of the material published between the above-mentioned dates. It is obvious that in the space allotted all material published during this period could not be commented on and it has been the intention of the authors to include only that material which seemed to be of greatest interest to the most readers and important to the aspects of the field of anesthesia covered

A total of 694 papers was reviewed. Data from 49 are included in the review.

## Inhalation Anesthetics

It is interesting that ether, the first adequate general anesthetic agent, first used for anesthesia more than 100 years ago, still remains the safest agent for the most patients in the hands of the greatest number of anesthetists. Cyclopropane, first used clinically by Waters, has gained much favor among many anesthetists but has some well-known disadvantages. Three agents with chemical configuration similar to cyclopropane have been tested in the laboratory during the year under consideration in the hope of finding one that might prove better and safer than cyclopropane

Krantz *et al.* (1) have observed the effects of cyclobutane. It is a gas under ordinary conditions of temperature and pressure, with an odor resembling that of cyclopropane. It is relatively insoluble in water and readily soluble in oil It is nonirritating to membranes of the respiratory passages and is capable of inducing anesthesia at a concentration of 20 to 40 per cent. The anesthesia produced is similar to that produced by cyclopropane. In dogs and monkeys under cyclobutane anesthesia, injections of epinephrine caused arrhythmias similar to those occurring under the same conditions when cyclopropane was the anesthetic agent. Studies on the liver have suggested that no hepatic damage follows use of cyclobutane. Its characteristics in general proved to be much like those of cyclopropane and it has been suggested that it is a safe enough agent to be given a clinical trial when an adequate supply becomes available.

Virtue (2) conceived the idea of trying cyclopentane and cyclohexane as anesthetic agents, chiefly because of the ready availability of these gases as by-products of petroleum. They were tested on mice and dogs, and after a thorough study neither was found to be a safe or satisfactory agent for surgical anesthesia.

After studying several physical methods for a constant determination of

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subcortex. The presence of a central effect from therapeutic doses of curare can only be presumed from his observations. There is probably more evidence against the central effect of curare than there is in favor of it, and until this highly controversial question has been more satisfactorily settled, Berman's conclusion that curare has a central effect must be viewed with suspicion.

In 1857 Claude Bernard found that, in curarized dogs, vagal stimulation did not cause bradycardia or asystole. Burstein *et al.* (7) reproduced this phenomenon consistently in eight dogs and later applied its principle to human beings. They mentioned two patients on whom dissections of the neck were being performed when troublesome carotid sinus effects manifested themselves by bradycardia and hypotension. The patients were given *d*-tubocurarine chloride intravenously and within 3 min. the carotid sinus effects were abolished. The amount of curare necessary in each case was sufficient to cause intercostal paralysis. If this is a consistent result of the administration of curare, it immediately becomes obvious that curare will be useful in combating certain troublesome reflexes so often encountered during certain types of surgery.

Curare has been successfully and safely used as an adjunct to most of the commonly used general anesthetic agents, but probably the two most commonly combined with curare are cyclopropane and pentothal sodium. Baird (8) was one of the first clinicians to recognize the potentialities of a combination of pentothal sodium, nitrous oxide, and curare and has reported a series of 3,480 cases in which this combination was used without an anesthetic death. He must certainly stand on his experience in speaking of the advantages and safety of this combination. To more than 95 per cent of the patients in his series these agents were administered by residents. His series includes patients who were from four months to 94 years of age. He stated that there are only two real contraindications to the use of this combination. They are (*a*) myasthenia gravis, and (*b*) inability to administer adequate artificial respiration through a patent airway. He pointed out the superiority of this combination for thoracic surgery and for cardiac surgery in children, especially for the operative correction in cases of the tetralogy of Fallot. He has used this combination in 40 cases in which this last-mentioned operation has been performed with no deaths, whereas previously, when he employed cyclopropane anesthesia for this operation, fatalities had occurred rather frequently.

This combination has much to be said for it, but its use certainly should be reserved for those experienced in it if the safety record of Baird is to be duplicated. In regard to contraindications to this method we would add a third to Baird's list, namely, bronchial asthma. In our experience, when bronchial spasm is precipitated in asthmatic persons by curare it is extremely persistent and difficult to relax and can be a real menace to the patient.

Stoelting *et al* (9) have reported the use of a new form of curare to produce relaxation during anesthesia It is the dimethyl ether of *d*-tubocurarine iodide and is said to be as effective as *d*-tubocurarine chloride as a muscle

ether tension in anesthetic mixtures, Faulconer (3) finally devised a method which is based on the principle that the speed of sound passing through a gas or a mixture of gases varies with the composition of this mixture. As yet this method is useful only in research, but with further refinements and simplifications it is hoped that the device might find practical application in the everyday practice of anesthesia. Later Faulconer & Latterell (4) reported further on the use of this so-called acoustic gas analyzer in connection with the Pauling oxygen meter and the Millikan self-compensating oximeter on 16 patients who were being given air-ether anesthesia. They found that application of a mask to the face of the patient reduced this oxygen tension [illegible]

the partial pressure of ether vapor under the mask to 100 mm. or more, and it was noticed that the average pressures of ether during induction of anesthesia were 35 to 75 mm. Some significant reduction in the oxygen saturation of arterial blood, which was definitely related to the changes in the oxygen tension under the mask, were observed. They found that the addition of as little as 500 cc. per min. of oxygen under the mask brought the oxygen saturation of arterial blood to normal and have recommended this procedure as a routine in all instances in which the semi-open air-ether method of anesthesia is to be used

Harger, Turrell & Miller (5) have described a viscosity effusion meter for constantly indicating the concentration of anesthetic gases. Their instrument is said to record accurately the concentrations of ether, cyclopropane, ethylene, and nitrous oxide in nitrogen or nitrogen and oxygen, and also will indicate the approximate concentration of oxygen in nitrogen. It may be modified to determine the concentration of any two of these gases in rebreathed air. In their instrument they made use of the fact that different gases have different densities and, therefore, the resistance created as the gases are sucked through capillary tubes varies with the gas mixture. The resistance for practical purposes, therefore, can be considered to be a product of the gas mixture, and calculations can be made on this basis. They described the use of their meter on six patients during surgical operations and analyzed the various readings obtained.

## Muscle Relaxants

It is not in the realm of this brief review to include a résumé of the many interesting reports of earlier investigations with curare and similarly acting agents, but instead to mention only the most interesting and important reports appearing in the year under consideration Recently Berman (6) reported the use of curare in psychiatric patients and implied that curare had a central effect. In 16 out of 19 patients a sedative effect was thought to occur, and he stated that this was due to a depressing effect of curare on the

cases as a substitute for *d*-tubocurarine chloride and found it satisfactory and without severe side effects. Hewer *et al.* (17) reported its use in 85 operative cases and found it a satisfactory relaxant, but relaxation comparable to that obtained with *d*-tubocurarine chloride could be obtained only with doses which caused respiratory paralysis. They used the antidote in eight cases, in three of which an alarming degree of circulatory collapse developed They concluded that the antidote, because of this tendency, is too dangerous to use in anesthesia practice. Davies & Lewis (15) and Hobsen & Prescott (18) found this agent to be a satisfactory relaxant when used to control the convulsions of electroshock therapy. No significant advantage over *d*-tubocurarine chloride was observed. The other new relaxant agent called "flazedil" has been described by Mushin *et al.* (19). The proper designation of this agent is tri-(diethylamino-ethoxy)-benzene triethyliodide. It has a curare-like action at the myoneural junction which is reversed by neostigmine. It is less potent than *d*-tubocurarine chloride and seems to have a slightly wider margin of safety between the relaxing dose and the dose causing respiratory paralysis. It causes less histamine to be liberated and has little paralyzing effect on autonomic ganglia. Side effects are unimportant. The only characteristic of this drug that seems to offer any advantage over *d*-tubocurarine chloride is its tendency to preserve respiration longer.

Much laboratory and clinical work will be required to prove the superiority of any of these new relaxant agents over *d*-tubocurarine chloride, and until this has been done curare still holds first place as a safe and effective muscle relaxant for use in anesthesia.

## Spinal Anesthesia

Since the advent of spinal anesthesia new trends in methods and agents have frequently been reported. In most instances it has been hoped that these new trends would help spinal anesthesia to better fulfill the requirements imposed on all methods in medicine, namely, adequacy and safety to the patient Procaine was the first anesthetic agent to be considered safe for intrathecal use but proved to be of too short duration to be of practical value in many instances As time passed, many new agents were proposed in an attempt to increase the duration of the analgesia In most instances increase in duration of analgesia was paid for by a sacrifice in the degree of safety to the patient since the newer and longer acting drugs proved to be more toxic than procaine Fractional spinal anesthesia introduced by Lemmon in 1940, though obviating some of the difficulties imposed on the spinal anesthetist, has retained only a certain limited measure of favor because of the technical difficulties inherent within the technique itself.

Roman & Adriani (20) have reported on the use of nupercaine for more than 5,000 instances of spinal anesthesia. They stated that no neurologic complications occurred within 14 to 16 days after anesthesia in any of their cases. After reviewing the literature they concluded that neurologic complications are no more frequent with nupercaine than with other agents, such as

relaxant, but does not cause the degree of respiratory depression that the latter drug does. They stated that when respiratory depression followed the use of dimethyl ether of *d*-tubocurarine iodide this depression was of a minimal degree. Milligram for milligram the new drug is more potent than *d*-tubocurarine chloride We have used this same drug in a fairly large series of cases and have not observed any significant difference in the respiratory depression caused by *d*-tubocurarine chloride and that of dimethyl ether of *d*-tubocurarine iodide.

Since Berger & Bradley (10) first reported the introduction of the muscle

short acting, must be given in large doses, and in some instances it has caused untoward results. In brief, it appears to have proved inferior to *d*-tubocurarine chloride as a muscle relaxant, and in addition the possibility of untoward effects constitutes another score against this agent. A fatal instance of anuria following the use of myanesin was reported recently by Goodier & Goodhart (11). Griffith *et al.* (12) have concluded that it is an unsatisfactory muscle relaxant, and enumerate some of the undesirable side effects such as thrombophlebitis at the site of injection, hemoglobinuria, and albuminuria.

Berger & Schwartz (13) have used myanesin in the oral treatment of spastic and hyperkinetic states and have been favorably impressed with the decrease in spasticity, increase in range of motion, decrease in involuntary movements, and relief of pain after a few days of medication. These effects are said to be due to the selective depressant effect on the central nervous system.

Schlan & Unna (14) have used myanesin for psychiatric patients and stated that it produced sedation without clouding of the sensorium in anxiety states, reduced spontaneous activity in certain types of psychoses, and was of marked benefit in prolonged alcoholic intoxication. It did not change chronic schizophrenic states. The pattern and duration of seizures in electroshock were unchanged.

Two new muscle-relaxing agents have been described in the year under consideration. One of these called "decamethonium iodide (bistrimethylammonium decane diiodide) or $C_{10}$," has been reported on recently in *Lancet* (15 to 18) It was first suggested in 1948 by Paton and Zaimus after a study of a series of polymethylene bistrimethylammonium compounds. It is said to be cheap and easy to prepare in a pure state It causes neuromuscular block which "appears to affect skeletal muscles more than respiratory muscles" (16). Its action is not reversed by neostigmine It liberates less histamine and has less paralyzing effect on autonomic ganglia than *d*-tubocurarine chloride. It is eliminated chiefly via the kidneys. The antidote is pentamethonium iodide, which has a potent effect in blocking autonomic ganglia and like tetraethylammonium bromide may cause a dangerous fall in blood pressure. Organe (16) reported the use of $C_{10}$ at operation in 150 unselected

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be necessary to answer this question. Gross *et al.* (27) and Leimdorfer & Metzner (28) have offered evidence that epinephrine itself has analgesic action and that this action is not an effect of vasoconstriction followed by ischemia. However, it seems unlikely that this analgesic effect of epinephrine is important in prolonging the effect of spinal anesthesia because of the small doses used intrathecally as compared with those of Leimdorfer & Metzner (28). Because of the normal variations in the reactions of different individuals to the effects of spinal analgesia and the frailty of human observation a true evaluation of the effects of adding vasoconstrictors to the spinal agent is extremely difficult and to date it is our opinion that proof of the true effectiveness of such a procedure has not, as yet, been established

### Procaine Used Intravenously

In the past few years, the intravenous use of procaine for therapeutic purposes has been supported rather enthusiastically by a few workers Although the therapeutic efficacy of procaine given intravenously is still doubtful or at least not universally accepted, it seems fitting that a few of the current views should be briefly mentioned herein.

The intravenous use of procaine was advocated by Bier in Germany in 1909. The agent was used as a local analgesic, and it was kept confined to the extremity by the use of an Esmarch bandage followed by a tourniquet. In 1940 one of us (Lundy) first used procaine intravenously to control pruritus associated with jaundice.

In 1947 Graubard, Robertazzi & Peterson (29) published a preliminary report on the intravenous use of procaine in 448 cases, in which 1,954 infusions of procaine were given without morbidity or mortality They described their so-called procaine unit as a basis for calculating dosage. This unit consisted of 4 mg. of procaine per kilogram of body weight dissolved in normal saline solution, to be given over a period of 20 min or longer. They were enthusiastic over the results of the treatment of a variety of conditions. More recently Graubard & Peterson (30) have reported on the therapeutic use of procaine in which the series of cases has been further evaluated. More than 20 pathologic conditions classified under the categories of traumatic, inflammatory, and miscellaneous were treated by this method. It is interesting to note the various and bizarre types of conditions that were included in their series and which, in many cases, were found to respond favorably to this treatment They stated that, in brief, the effectiveness of this type of treatment in the pathologic state is based on the permeability of the capillary membrane to colloids as well as to ions In traumatized tissue, concentration of procaine is from seven to eight times more than in normal tissues due to increased capillary permeability. These reports reflected, to a degree, the marked enthusiasm of Graubard and his associates and their opinions and conclusions are based on honest and sincere appraisal of their results, but whether or not others will be able to reproduce some or all of their results is a matter of speculation, and only time and further trials by more and more

investigators will decide the place of procaine given intravenously in treatment of the various conditions enumerated in their reports.

Rovenstine & Papper (31) and Burstein (32) have used procaine as a therapeutic agent in many conditions and have been encouraged by the results of many of their experiments. Burstein (32) stated that in treating cardiac arrhythmias developing while the patient is under anesthesia, which are probably due to sensitization of the cardiac conduction mechanism, the drug of choice is procaine. He also stated that it has a place as a prophylactic agent during anesthesia, to be used to prevent arrhythmias in patients with cardiac disease. Procaine and diethylamino-ethanol (33) have both been used successfully in correcting and preventing cardiac arrhythmias. The effects of the latter are said to last longer but larger doses are required. The mechanism of the effects of these agents on the heart has not been explained.

Papper and co-workers (33) have concluded that procaine given intravenously for the most part is useful as an analgesic agent and in general is chiefly worth while for relief of pain associated with trauma and inflammation. The analgesic action is said to be due to leakage of procaine or its products of hydrolysis through the injured capillaries into the perivascular space where the nerve endings are bathed. It also has been suggested that its analgesic action is due to a central effect (34).

In regard to the fate of procaine administered intravenously (33, 35) it has been shown that only about 2 per cent of the amount injected can be recovered as such from the urine. The remainder is hydrolyzed to *p*-aminobenzoic acid and diethylamino-ethanol. About 90 per cent of the *p*-aminobenzoic acid portion can be recovered from the urine as such or in its various conjugates. Only about 33 per cent of the diethylamino-ethanol can be recovered unchanged. It has been postulated, therefore, that the other 60 to 70 per cent is further metabolized in a manner as yet unknown. By calculating the rate of blood flow through the liver and the rate of hydrolysis of procaine *in vitro*, it was decided that the liver is not the chief seat of destruction of procaine but that plasma hydrolysis probably accounts for the major portion of this process This fact may be important in determining the safety of any local anesthetic agent and most especially when the intravenous route of administration is considered.

Papper, Brodie and co-workers (33, 35) have postulated that the *p*-aminobenzoic acid is probably responsible for none or very little of the effects of procaine and that by far the major portion of the activity of procaine comes from the diethylamino-ethanol fraction. It is obvious that further studies will be necessary in order to learn with certainty the more exact pharmacologic effects of procaine and its metabolites.

Jacoby and co-workers (36), prompted by the recent trend toward the intravenous use of procaine, carried out studies on human beings, rats, and dogs, in which the excretion of bromsulfalein and the hippuric acid tests were used to test liver function They concluded that repeated massive doses of procaine caused no damage to the liver, spleen or heart of rats and dogs.

Their conclusions were on the basis of liver function tests in acute and subacute experiments in which histologic studies were made. The liver function tests performed on human beings were on patients who had received repeated doses of procaine intravenously for the control of postoperative pain. The results of these tests were in complete accord with those of their studies on animals.

Olsen *et al.* (37) have reported on the intravenous use of procaine in the treatment of carbon monoxide asphyxia. They stated that the rationale for this type of treatment is based on an analogy that can be drawn between cerebral asphyxia and local asphyxia elsewhere as seen in embolism, toxic or reflex anuria, angina pectoris, decubitus and stasis ulcers, Raynaud's disease, frostbite, and pregangrenous conditions, all of which have been said to have shown improvement on procaine therapy. They reported several cases of carbon monoxide asphyxia in which intravenous administration of procaine was employed, and stated that there was a marked consistency of correlation between the clinical symptoms and the electro-encephalographic findings, even in patients who made rapid recoveries They were greatly encouraged by their results and stated that procaine was a worth-while therapeutic measure in cases of carbon monoxide asphyxia.

### Arterial Transfusions

Although the subject of intra-arterial transfusions is not new, some good recent contributions have been made by Hale (38), Page (39), Robertson, Trincher & Dennis (40), and Stevenson (41), and it seems fitting that a review of this interesting procedure be included.

It has been reported that Crile gave one intra-arterial transfusion in 1903 (41), that Davis used intra-arterial infusions of saline solution in 1937 (40) and Brillo, a Russian, gave blood by this route in 1939 (40). In this country Kohlstaedt and Page were said to have used intra-arterial transfusions in dogs in experimental shock. Page (39) stated that later Page, Seeley, Kohlstaedt and Glasser all contributed to the development of this method. Gardner (42), in 1946, made the first use of controlled hypotension in the course of an operation for meningioma of the olfactory groove, and since this time a number of reports of the clinical application of arterial transfusions and controlled hypotension have been seen in the literature.

Page (43) recognized the advantage of intra-arterial transfusions and stated that the infusion carries blood immediately to the myocardium and medullary centers and rapidly restores blood pressure to normal The state of controlled hypotension during certain operations, with the reinfusion of the withdrawn blood at the time when bleeding had been well controlled, as suggested by Gardner (42), offers the counterpart to the usefulness of intra-arterial transfusion itself.

Stevenson (41) listed several precautions to be observed if this type of infusion is used. He stated that an absolutely aseptic and clot-free technique must be used in order to obviate technical difficulties Hale (38) has well

investigators will decide the place of procaine given intravenously in treatment of the various conditions enumerated in their reports.

Rovenstine & Papper (31) and Burstein (32) have used procaine as a therapeutic agent in many conditions and have been encouraged by the results of many of their experiments. Burstein (32) stated that in treating cardiac arrhythmias developing while the patient is under anesthesia, which are probably due to sensitization of the cardiac conduction mechanism, the drug of choice is procaine. He also stated that it has a place as a prophylactic agent during anesthesia, to be used to prevent arrhythmias in patients with cardiac disease. Procaine and diethylamino-ethanol (33) have both been used successfully in correcting and preventing cardiac arrhythmias The effects of the latter are said to last longer but larger doses are required. The mechanism of the effects of these agents on the heart has not been explained.

Papper and co-workers (33) have concluded that procaine given intravenously for the most part is useful as an analgesic agent and in general is chiefly worth while for relief of pain associated with trauma and inflammation. The analgesic action is said to be due to leakage of procaine or its products of hydrolysis through the injured capillaries into the perivascular space where the nerve endings are bathed. It also has been suggested that its analgesic action is due to a central effect (34).

In regard to the fate of procaine administered intravenously (33, 35) it has been shown that only about 2 per cent of the amount injected can be recovered as such from the urine. The remainder is hydrolyzed to *p*-aminobenzoic acid and diethylamino-ethanol. About 90 per cent of the *p*-aminobenzoic acid portion can be recovered from the urine as such or in its various conjugates Only about 33 per cent of the diethylamino-ethanol can be recovered unchanged. It has been postulated, therefore, that the other 60 to 70 per cent is further metabolized in a manner as yet unknown. By calculating the rate of blood flow through the liver and the rate of hydrolysis of procaine *in vitro*, it was decided that the liver is not the chief seat of destruction of procaine but that plasma hydrolysis probably accounts for the major portion of this process This fact may be important in determining the safety of any local anesthetic agent and most especially when the intravenous route of administration is considered.

Papper, Brodie and co-workers (33, 35) have postulated that the *p*-aminobenzoic acid is probably responsible for none or very little of the effects of procaine and that by far the major portion of the activity of procaine comes from the diethylamino-ethanol fraction. It is obvious that further studies will be necessary in order to learn with certainty the more exact pharmacologic effects of procaine and its metabolites.

Jacoby and co-workers (36), prompted by the recent trend toward the intravenous use of procaine, carried out studies on human beings, rats, and dogs, in which the excretion of bromsulfalein and the hippuric acid tests were used to test liver function. They concluded that repeated massive doses of procaine caused no damage to the liver, spleen or heart of rats and dogs.

TABLE I

Observations of Five Groups of Investigators on Methadon

| | Analgesia compared to morphine | Euphoria and hypnotic effects | Tolerance and addiction | Side effects | Miscellaneous |
|---|---|---|---|---|---|
| Christensen & Gross (44) | Three times that of morphine | Little sedation | | Slight—only small doses were used | Duration shortened by adding atropine or scopolamine; neostigmine increased duration of analgesia |
| Kirchof & David (45) | About same as morphine | Rarely seen | Addiction not seen but possibility was admitted | None serious—seen in 14 5 to 17 per cent, nausea most common, more common in oral use | Majority of actions resemble those of morphine |
| Isbell (46) | About same as morphine | | Addicting to a lesser degree than morphine | Reactions of about same severity and frequency as with morphine | Recommended for painful conditions requiring relief for longer periods and when patient is addicted to opiates |
| Tainter & Buchanan (47) | 0.48 mg. = 1.65 mg morphine three to four times that of morphine | Not good | Capable of causing addiction | No serious toxic effects in usual doses; large doses caused effect like morphine; mostly vertigo and nausea | Methadon 10 8 times as toxic as morphine in mice |
| Batterman & Oshlag (48) | Same as morphine | Drowsiness frequently seen | Possibility of addiction is real—tolerance (?) | Almost none in hospital patients when given parenterally | Good for controlling withdrawal from opiates |

illustrated and described the apparatus that he used. It should be obvious that a simple and fool-proof apparatus is desirable. It seems that the apparatus described by Hale fulfills these criteria. Stevenson further suggested that short stabilizing periods during the hypotensive state permit good estimates of the cardiovascular system and that frequent checks of blood pressure during this period help in the prevention of sudden serious vascular collapse. He warned against beginning the reinfusion under a pressure which is more than 50 mm. of mercury higher than that of the recipient because the cardiovascular system might react in an abnormal manner with a sudden rise in venous pressure and that death might follow. The pressure used in the reinfusion should be started at a figure only slightly above the arterial pressure of the recipient and gradually increased.

Page (39) suggested that intra-arterial transfusion should be employed: (*a*) to restore blood volume rapidly after severe bleeding or crushing; (*b*) to maintain a hypotensive state when it is indicated; (*c*) to control pressure and blood volume during cardiac and vascular surgery; (*d*) for purposes of resuscitation in severe hypotension—the benefits here occur from perfusion of the coronary arteries and vital medullary centers—and (*e*) to maintain arterial pressure and to aid in the detection of bleeding points in patients moribund after severe injury.

Robertson *et al.* (40) have mentioned what they considered to be contraindications to the use of intra-arterial transfusion, e.g., (*a*) it is to be used only as an emergency measure because of the need for arterial puncture; this often means the sacrifice of the artery; (*b*) nothing can be expected from this procedure in terminal stages of an acute or chronic illness as the response will be only temporary; (*c*) its use in heart disease or heart failure is debatable; and (*d*) obviously it is more effective when hemorrhage is controlled.

From the foregoing summary it can be said that intra-arterial transfusions as described offer some real and definite advantages. The indications and contraindications seem to be clear-cut. In the hands of the experienced, intra-arterial infusion of blood or plasma should be a relatively safe and extremely effective procedure. Conversely, in inexperienced hands it is an extremely dangerous procedure.

## Newer Analgesic and Sedative Drugs

In recent years considerable interest has been shown in some of the newer analgesic drugs. It has been hoped that a good substitute would be found for morphine. Special interest has been shown in methadon (6-dimethylamino-4, 4 diphenyl-3-heptanone hydrochloride). This drug promised to be a good substitute for morphine, retaining most of its advantages, and at the same time not possessing certain of its undesirable properties. Many contributions on this subject have appeared in the literature since the introduction of methadon and it is hoped that a summary of five articles appearing in the literature during the past year will help to crystallize in the minds of the reader certain facts in regard to this analgesic drug. These articles are by

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Christensen & Gross (44), Kirchof & David (45), Isbell (46), Tainter & Buchanan (47), and Batterman & Oshlag (48). The findings of these workers are summarized in TABLE I.

As can be seen in TABLE I it is quite universally agreed that methadon has definite analgesic properties which, when compared to those of morphine on a milligram for milligram basis, are variably rated. Some investigators rate its analgesic potency as equal to that of morphine, while others state that it is three to four times as potent. All agree that methadon has almost no sedative or euphoric effect. Tolerance and addiction to methadon are not seen as frequently as with morphine, but the danger of their occurrence is real. In regard to the side effects Kirchof & David (45) have given a fairly complete list which includes nausea, diaphoresis, respiratory depression, vertigo, pruritus, lethargy, tingling, euphoria, and heart burn. Nausea and vertigo were the two most common side effects None of these side effects has been considered to be serious and most investigators have agreed that they occur much more frequently among ambulatory patients being given oral medication than among patients confined to bed who receive medication parenterally.

Although in some respects methadon has fallen short of being an ideal substitute for morphine, it still remains a good analgesic and should be useful in controlling withdrawal symptoms in cases of morphine addiction, for patients who cannot take opiates for one reason or another, for patients who need an analgesic for a longer period of time than morphine can be safely given, and for controlling the cough reflex.

Wyngaarden *et al.* (49) have reported their investigation of several thiobarbiturates. They pointed out that such drugs as evipal, pentothal sodium, thioethamyl, and kemithal have certain undesirable characteristics such as cumulative effects, persistence of the laryngeal reflex, respiratory depression, lack of analgesic activity, and a possible adverse effect on cardiac activity They hoped to find a thiobarbiturate not possessing the disadvantages mentioned Of those studied one showed promise. This was sodium 5-allyl-5-(1-methyl-butyl)-2-thiobarbiturate (surital) They observed that induction and recovery were rapid, and relatively small doses were required In fact the potency is said to be one and one-half times that of pentothal sodium. They observed that the cumulative effects were minimal and that the respiratory depression was similar to that seen with pentothal sodium.

From the contents of their report it is our opinion that surital probably has some possibilities as an intravenous anesthetic agent, but until more work has been done with surital we must assume that to date pentothal sodium remains the safest and most effective anesthetic agent for intravenous administration.

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# RADIOLOGY AND RADIOACTIVITY

## Radiobiology in the Service of Medicine[1]

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The science and art (technique) of radiobiology are developing rapidly. What is both new and important is hard to select. What one fixes on as present day attainment may promptly be superseded. One would not care to predict how much of what one writes today will be worth reading tomorrow.

The researches are legion concerning histologic, cytologic, and genetic effects of radiation, and the differential action of the several kinds of radiation. Radioisotopes give new tools, but the field has long been well cultivated with the older tools, viz., x-rays and radium. Modern texts by Bloom (103) and Lea (104) should be consulted.

One new trick is intriguing, namely, the measurement of small quantities of an element in a tissue by irradiating it with neutrons and measuring the induced radioactivity Brues (1) thinks iodine is measurable this way in tinier amounts than microchemical methods will detect. Tobias (2) considers several elements.

Tracer uses for clinical diagnosis, clinical investigation, and physiological research form the broadest field for radioactive isotopes——the most heterogeneous, the most difficult to analyze and report upon, and, in the opinion of this reviewer, far and away the most promising for future developments. If and when atomic energy produces any revolutions in medical practice it is likely to be by furnishing the tools to solve some fundamental problems of physiology and pathology In these fields, one readily believes, the sky is the limit. As yet the clinical diagnostic uses are not numerous.

### RADIOISOTOPES IN CLINICAL DIAGNOSIS

#### Thyroid Function And The Diagnosis Of Graves' Disease

Radioactivity in the neck, followed usually with a Geiger counter, rises rapidly after the patient has drunk some $I^{131}$. The usual test dose is 100 $\mu$c., though some (3) prefer 40 $\mu$c to avoid possibility of harm should the uptake prove high and the gland small. In cases where thyroid operation or biopsy is contemplated 500 or 1,000 $\mu$c. is advisable in order to get good radioautographs.

Myxedema and cretinism show only a few per cent uptake. Normal thyroids run 10 to 35 per cent, hyperthyroids 25 to 90 per cent. The overlap means that some cases are equivocal on the basis of this test alone Measurements of serum iodine may help in the diagnosis Thyroiditis shows low uptake. Adenomas usually show lowered uptake, though some show increase,

[1] This review covers the period from approximately January, 1947 to July, 1949.

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flesh of 7 mm. The x-rays (*bremsstrahlung*) that it induces are weak and poorly detected by a counter; therefore, deep-lying tumors will not reveal themselves. The counts over a superficial tumor may run half again as many as over the surrounding normal breast. Unfortunately, inflammations can also pick up $P^{32}$, and so can normal lymph nodes.

*Metastases.*—A few cases of thyroid cancer have taken up enough $I^{131}$ to render remote metastases detectable (16). Other cancerous metastases, if sufficiently superficial, may possibly be detected by uptake of $P^{32}$.

### CIRCULATION

*Blood volume.*—Autologous erythrocytes labeled by incubating with $P^{32}$ are an ideal material for determination of blood volume by dilution (17). This method has been validated by comparing with erythrocytes labeled with $Fe^{59}$ (18).

Minute volume and the thoracic pool can be calculated from the curve of changing activity in arterial blood after injection of $P^{32}$ labeled red cells (19)

*Heart disease.*—A brief intravenous injection of $Na^{24}$ with measurement of the rate of rise and fall of activity over the heart is reported to give curves characteristic of the type of cardiac disease (20). A second peak of activity marks the passage of the labeled portion of blood through the lungs and into the left side of the heart

*Peripheral circulatory impairment.*—Several workers have measured the rate of penetration of injected $Na^{24}$ into the limb. Apparently 200 $\mu$c. of $Na^{24}$ can be safely used for such diagnostic purposes. Even this short-lived isotope is not without danger, however, A fatal thrombocytopenic purpura is reported following a total of 202 mc. over a period of five months. Total body irradiation was calculated to be 285 r (21)

One can also measure the rate of escape of $Na^{24}$ from a local intramuscular injection (22), a procedure which has the advantage of requiring a much smaller quantity of $Na^{24}$. The author hopes that $I^{131}$ will be used in this way, for it is much more available than the $Na^{24}$ (see p 328)

Blockages in larger arteries are easily demonstrable by arteriography (i e , clamp the femoral artery and inject a few cubic centimeters of thorotrast into the distal segment and make roentgenograms). In venous thrombosis, venograms by peripheral venous injections of diodrast are useful; but for peripheral arterial disease, the radioisotope method alone seems able to give quantitative results

### FUNDAMENTAL STUDIES

A great variety of studies concerning enzyme action, protein and lipoid metabolism, the nucleic acids, photosynthesis, etc., have been reported. Few of these seem immediately applicable to clinical medicine The principal tracers used are $P^{32}$, $S^{35}$, $C^{14}$, and the stable (heavy) isotopes $N^{15}$ and $D^2$ (deuterium or heavy hydrogen)

*Heavy isotopes*—The stable isotopes present considerable technical dif-

and an occasional small adenoma may have a specific uptake very much higher than normal thyroid. (4). Radioautographs show the $I^{131}$ in the cells and in the colloid The activity of the acini varies, a highly active vesicle sometimes lying next to one that has taken up no iodine.

The thyroid begins to take up iodine between the 12th and 14th week of fetal life (5).

Plasma iodine greater than 35 μg. per 100 cc. blocks organic binding of iodine in the thyroid (6). Patients who have been on iodine therapy may be weeks recovering their ability to take up iodine in the thyroid (3). Priodax and other iodinated substances used in diagnostic tests interfere similarly

*Antithyroid drugs.*—Stanley & Astwood (7) rated 32 compounds for effect on iodine uptake. A patient who has been on propylthiouracil therapy will bind but little iodine, but will recover his uptake capacity in a few days after stopping the drug There are antithyroid foods, too, e g , rutabaga and other members of the cabbage family, and others (8).

charge a great deal of it into the blood again (9).

Apparently iodine enters in several steps. (*a*) mere binding of the iodide ion, (*b*) oxidation of iodide ion to atomic or molecular iodine which conjugates with a protein and splits off as diiodotyrosine [chromatographic evidence also of monoiodotyrosine is reported (10)], and (*c*) formation of thyroxine from the diiodotyrosine. The plasma contains more thyroxine than diiodotyrosine, the thyroid vice versa The thyroid does not take up thyroxine from the blood

The various antithyroid drugs have greatly different relative efficiencies among different animals, even among different mammals (11).

*Iodine clearance*—It may be advantageous to calculate uptake and excretion in terms of cubic centimeters of blood cleared per minute by thyroid and kidney Clearances for thyroid may average 16 cc per min for normal glands, and from 200 to 1,400 cc. per min for toxic glands (12)

## Neoplasms

*Brain tumors*—Fluorescein has the remarkable property of staining brain tumors If iodinated with $I^{131}$, the radiation renders the tumor detectable (13). Reports show a moderate percentage of success in diagnosing and

ance to the surgeon (14) These special Geiger tubes are not yet on the market

the surface or the radiation cannot escape, for it has a maximum range in

be distinguished by counting methods This is a remarkable example of the use of two isotopes of the same element in the same tracer experiment.

*Zinc.*—It has been discovered that white blood cells contain about twice as much zinc (25) as the red cells, while leukemic white cells lack zinc. In a remission the zinc content rises again. The clinical significance and usefulness of this is not yet apparent. Zinc therapy, stable or radioactive, has not yet been reported.

*Arsenic.*—Because of the long time clinical use of arsenic in the leukemias, $As^{76}$ has been used for metabolic and therapeutic studies (26), but clinical application (27) seems as yet no more promising than $P^{32}$.

*Gold.*—Radioactive gold sols and solutions are available and have been studied to a certain extent (28). It seems plausible that something will come of their use in studying the mechanism of action of gold in arthritis, but no clinical application is as yet forthcoming.

## THERAPY WITH RADIOISOTOPES

Since few radioisotopes are proving useful as therapeutic agents, it still looks as if any revolutions in medicine will come from the tracer uses in fundamental research.

### Iodine

*Iodine collects rapidly and almost exclusively in the thyroid. Internal* irradiation is equivalent to 160 r for a concentration of 1 μc. per cc. (29). This is calculated for the isotope $I^{131}$ with half-life of eight days. It is mostly due to the beta rays, the gamma rays being so penetrating that they escape with but little absorption in the few centimeters thickness of even a large thyroid.

*Graves' disease.*—Overactive thyroid glands have been successfully treated by many workers who report on a total of several hundred cases Of various reviews, one might cite Kelsey (30) and Curtis (31). It might still be maintained with reason that thyroidectomy is the treatment of choice. Nevertheless, the art of handling hyperthyroidism with $I^{131}$ has progressed, and the large majority of cases have done well. If control proves incomplete, the patient can be treated again. Estimate of insufficiency of treatment should not be made for about three months, on account of the store of thyroxine which requires a long time for utilization (31) Incidence of persistent hypothyroidism or actual myxedema (32) may be no higher than from surgery (33) Malignant exophthalmos is a rarer sequel than after surgery, it is said, without very good proof. The parathyroids are not endangered, nor the recurrent laryngeal nerves. The irradiation required is of the order of 6,000 r (29) The dose to give this is calculated (29) from several factors, namely: (*a*) the percentage uptake of a preliminary test dose (say 100 μc ) as measured by the radioactivity accumulating in the neck (estimation from urinary excretion has been abandoned as undependable), (*b*) the rate of disappearance from the neck, called "effective half-life," which is usually five or six days compared to physical half-life of eight days, and (*c*) the estimated volume of the thyroid (by palpation). It is ordinarily given by mouth. Iodine

ficulty for tracer use, and most isotope laboratories are using only the radioactive ones Stable isotopes are measured by specific gravity techniques or with a mass spectrograph, which costs some thousands of dollars. Moreover, the measurements are less delicate and less rapid than for radioactive tracers.

*Carbon.*—$C^{14}$ has not yet been cleared for use in man because of its long half-life (no appreciable decay during a human lifetime) and present uncertainty whether the small amount which is not promptly excreted as $CO_2$ from the mammalian body might remain concentrated in some vital spot. The bad experience with radium, which remains concentrated in the bone and destroys the blood-forming organ, even in a fancifully small total amount (a few micrograms), has made us very wary of long-lived isotopes If one can make the synthesis, $C^{14}$ can be used to label any organic compound in any chosen group. Acetic acid, for example can be made "isotopic" in either the carboxyl or the methyl group. For biochemistry, $C^{14}$ would appear to be the ideal tracer.

*Iron.*—Natural iron irradiated in the pile produces a mixture of $Fe^{55}$ of four year half-life and $Fe^{59}$ of 46 day half-life in nearly equal activities. The long-lived one is considered hazardous for human use. Using iron enriched in the $Fe^{58}$ stable isotope, Oak Ridge has made some $Fe^{59}$ with but little $Fe^{55}$. $Fe^{59}$ can also be made in the cyclotron. Recently the Atomic Energy Commission has promised to market $Fe^{59}$ free or nearly free of $Fe^{55}$.

It is interesting to review some features of iron metabolism. Iron is remarkably conserved
are being continually
right back into red cel[illegible]
*designated IV-7 (3 per cent of plasma proteins) which it ordinarily saturates* about 30 per cent. The total amount of iron in the plasma is only some 5 mg. compared to the 2 to 3 gm in the red cells The turnover rate in the plasma is therefore very rapid indeed, shown nicely by tracer studies (23). About 75 per cent of tracer iron eventually appears in the red cells, corresponding to the partition of iron between red cells and other stores.

The "utilization curve" of red cells accumulating the tracer is steep and high in hemorrhagic and iron deficiency anemias, but flat and low in hemochromatosis (23). The degree of saturation of the iron-binding globulin is different in different diseases, being nearly complete in hemochromatosis, for example. The turnover rate in the plasma is astonishingly rapid in polycythemia. Such tracer studies might develop into clinical tests for the differential diagnosis of anemias.

The iron concentration in intestinal epithelium regulates the absorption of iron. Iron from breakdown of red cells is utilized for making new red cells twenty times as efficiently as iron taken by mouth. The nonviable cells in transfusions of stored blood are removed in a few hours, if there are not too many of them. A 70 per cent survival of transfused red cells is the least that is safe (24) This latter conclusion resulted from a study made by tagging some of the recipient's *cells with $Fe^{55}$ and tagging transfused cells with* $Fe^{59}$. The former gives x-rays, the latter beta and gamma rays,

*Topical uses of radio-phosphorus.*—A measured amount of $P^{32}$ absorbed in blotting paper is described as an elegant method of superficial irradiation (43), as for epitheliomas of skin. It gives only beta rays and these are mostly absorbed in the first few millimeters of flesh.

### Radioactive Colloids

Colloidal gold, chromic phosphate, and others given intravenously are picked up by the reticuloendothelial system, and if radioisotopic, irradiate the liver, spleen, and bone marrow selectively (44) Clinical usefulness has not been proven. Such radioactive colloids have also been injected into tumors and in the neighborhood of lymphatic metastases in the hope of destroying them (45) Similarly, radioactive silver has been injected into tumors in the hope that it would be locally bound by the protein and so irradiate the tumor from within (44).

Radioactive organ-specific antibodies have been prepared, but none that are useful in therapy. Iodinated antikidney serum is shown by radioautographs to localize in the glomeruli (46).

### Others

*Arsenic.*—Radioarsenic has been studied in animals and man, because of its use in leukemias (27, 47). No therapeutic recommendations have resulted.

*Cobalt*—$Co^{60}$ gives a soft beta radiation and two hard gammas, the latter equivalent to filtered x-ray at two megavolts Oak Ridge has reduced the price to five dollars per curie in large lots, which may induce the design of gamma ray "cannons" to compete with megavolt x-ray installations.

Beads, wires, and needles of $Co^{60}$ have been worked with as inexpensive substitutes for interstitial and intracavity radium. A cobalt nickel alloy[2] is more tractable for fabrication than pure cobalt. The pieces can be machined "cold" and then activated in the pile, Oak Ridge making a charge of 43 dollars per month for neutron irradiation of small quantities Some advise that $Co^{60}$ wires or needles be enclosed in nickel tubing (hypodermic needle tubing) to stop the beta rays One author describes filling a rubber balloon with solution of $Co^{60}$ chloride for internal irradiation of bladder tumors (48).

*Alpha ray therapy.*—Radon ointment made by absorbing small amounts of radon in vaseline has been promoted for the treatment of indolent ulcers, such as varicose ulcers and roentgen ulcers For the latter it seems quite illogical, yet several workers report good results in cases otherwise quite obdurate (49). This and thorium X (similarly promoted in England) are the sources of alpha rays

*Beta ray applicator, ophthalmic*—For a couple of decades a few therapists have used radon bulbs of high activity for topical application (50) Recently such concentrated beta ray therapy has been facilitated by the marketing of a Radium D applicator (51), offered particularly for use in benign ocular

[2] "Cobanic," a 40–60 alloy of cobalt and nickel is obtainable from Wilbur B. Driver Co, Newark, New Jersey.

and goitrogenic (antithyroid) drugs and foods preclude success, of course (see under THYROID FUNCTION AND THE DIAGNOSIS OF GRAVES' DISEASE), but propyl thiouracil can be given after the $I^{131}$ is well bound in the gland without driving it out too badly, so that the thyrotoxicosis can be ameliorated whilst awaiting the result of the internal irradiation. Pregnancy is a contraindication, for $I^{131}$ collects in the fetal thyroid after the third month of gestation (5) and could destroy it. The stomach and salivary glands pick up $I^{131}$ and excrete it (34), but no harm has been reported As a palliative method in heart failure (35), the intentional production of hypothyroid state by $I^{131}$ might be as successful as by surgery.

*Cancer of thyroid*—About 10 per cent of thyroid cancers take up iodine A few cases of successful control of thyroid cancer with metastases are reported (36) It appears necessary to obliterate the normal thyroid surgically *or by giving a large dose of $I^{131}$ before giving the definitive dose for the cancer.* A couple of cases are reported where a cancer, originally showing no uptake, later "learned" to take up iodine and responded to treatment with $I^{131}$ Thyroidectomy, thyrotropic hormone, thiouracil treatment over long periods of time, prolonged diuresis, and x-ray treatment of the tumor have all been reported as hopeful for increasing the avidity of thyroid cancer for iodine (37). There is a correlation between the histologic type of tumor and the likelihood of its taking up iodine: most likely in metastasizing adenoma, little likely in more undifferentiated types, most unlikely in papillary and large-cell types. Axelrod (38) gives a good review

Very large doses of $I^{131}$ have been used in attempts to control thyroid cancer, 100 mc. in some cases, 200 mc in a few These produce symptoms of radiation sickness due to the total body irradiation accumulated before the body has excreted what fails of sequestration in the thyroid In a few the bladder has been sufficiently irradiated to give transient soreness No disasters of bone-marrow destruction have been reported

## PHOSPHORUS

*Leukemia.*—Chronic myelogenous and lymphatic leukemias have been treated with $P^{32}$ by many workers (39) with good palliation No cures have been attained. Whether it is better on the whole than total-body x-ray is yet to be shown. Where local irradiation seems desirable, x-ray would be chosen Acute leukemias do not respond to any type of irradiation, and no reports on $P^{32}$ have changed this conclusion

*Polycythemia.*—Some workers (40) would call $P^{32}$ the method of choice for control of polycythemia. The dose is 4 to 6 mc. It is not curative, but remissions may be fairly enduring (a year or more).

*Metastatic Cancer.*—$P^{32}$ has produced palliation in a few cases, but the tumor must be extremely radiosensitive to give any promise at all, for cancer picks up little more $P^{32}$ than the bone marrow

*Gonads*—Testicular injury (histological) follows regularly on therapeutic doses of $P^{32}$ (41).

*Calculi.*—Urinary calculi have become radioactive after $P^{32}$ therapy (42).

trons are to be classed with beta rays in this regard. Neutron rays, whose energy is absorbed mostly by colliding with hydrogen nuclei, are to be classed with proton rays. The biologic effectiveness increases with specific ionization, but not in a regular or predictable way (56). Ion for ion, neutron rays are twice as effective as x-rays for some biologic processes, 20 times for others. The effects are additive (57), or maybe not precisely additive (58).

*Radioisotopes.*—There are 96 known elements, half a dozen of which are man made and not known in nature.[4] Their differing chemical qualities depend on their differing numbers of electrons grouped about the central nucleus. But a nucleus, to have a given positive charge and hence hold a given number of electrons about it, need not necessarily have a unique weight. The number of (charge carrying) protons in the nucleus is definite, of course, for a given element, but the number of (chargeless) neutrons can vary within limits. Nuclides (i.e., aggregations of atoms of identical composition) having the same number of protons (i.e., the same element) but differing in the number of neutrons are called isotopes (meaning "the same place in the periodic table").

Many elements are found naturally to be a mixture of several isotopes. Natural isotopes are stable or very long-lived or they would not be here. The exceptions are those that are being continually replenished by radioactive decay of long-lived isotopes (i.e., short-lived daughters of long-lived parents).

Nuclides which disintegrate spontaneously with production of an energetic radiation and thus turn into another element are called radioactive isotopes. If the word nuclide had been invented in time, we no doubt would by preference have called them radioactive nuclides, but the term radioactive isotopes is by now thoroughly established.

By bombarding (irradiating) the natural elements with high speed positive ions of various sizes in a cyclotron, or with neutrons in a cyclotron or pile, or even with sufficiently energetic beta rays or x-rays, or by induction of atomic fission, many isotopes of all the elements can be artificially produced. The total number of isotopes now known is something over 1,000, most of which are radioactive. If it were not for this they would be hardly known, for they are produced usually in very tiny amounts (measured by weight). Chemically they are identical with other isotopes of the same element. The exceptions are deuterium, the stable heavy isotope of hydrogen and tritium, the radioactive heavy hydrogen, where the difference in mass is so overwhelming, i.e., 2:1 and 3:1 respectively, that many chemical, especially biological, reaction rates are greatly altered. In fact heavy water ($D_2O$) is a deadly substitute for ordinary water ($H_2O$) in living systems (past a moderate percentage). This was demonstrated quite early (59).

*Millicurie, symbol mc*—(One curie, symbol c., equals 1,000 mc. One microcurie, symbol $\mu$c., equals 0.001 mc.) This is the usual unit of measure-

[4] Element 97 has just been reported as having been made by Seaborg at the University of California.

conditions such as corneal opacities and vascularization. Radiostrontium has been suggested as a less costly substitute.

*Nasopharyngeal irradiation.*—Much has been written about irradiation of the nasopharynx to relieve deafness in childhood due to eustachian obstruction from hypertrophic lymphoid tissue, and to forestall adult deafness Recently the use of a narrow radium applicator inserted through the nose into the mouth of the eustachian tube has gained considerable favor as a way to accomplish this (52). The filter is thin (0.3 mm. monel) letting hard beta rays through. The effect is marked though local. Some reports are enthusiastic. Qualms are expressed by some on account of the known capacity of radiation to induce cancer years afterward. External application of x-rays is perhaps as effective and safer (53).

## DEFINITIONS

Radiobiologists use a number of esoteric terms. A small glossary (54) has been printed by the Council on Physical Medicine of the A.M A. and can be obtained from them. For two years the National Research Council has been working on a glossary for the A.E.C. This should soon be available. The United Nations has printed a glossary of 400 words and terms in the five official languages A few terms are rather widely misunderstood and are therefore explained here.

*Roentgen*—Roentgen, abbreviated r, simple lower case r without a period. This is a unit of exposure to x-rays (and by extension, to gamma rays). Its international definition can be paraphrased thus: An exposure of 1 r is such as would produce 2,100,000,000 pairs of ions in 1 cc. of air, (standard temperature and pressure). Note that one does not add the exposures on two fields of irradiation on a patient (55), any more than one would add the exposures on two successive pictures taken in a camera.

*Tissue dose.*—This is often at present given in r, but there is a movement afoot to recommend its recording in terms of the significant quantity, i.e., the ionization produced by the radiation absorbed. Moreover it will probably be found wise to define it in fundamental physical terms, i.e., as ergs per cubic centimeter or ergs per gram. Tissue doses from several exposures are additive when referring to the same point or region

Tissue dose (i.e, ionization of flesh) comes also from irradiation by particles (beta rays, alpha rays, proton rays, neutron rays, deuterons and heavier ions in the beam of a cyclotron, fission fragments). Therefore such irradiations can be made commensurable with x-rays in terms of tissue dose. The rep, promulgated among Health Physics Departments of the Manhattan District, is a unit of tissue dose, now defined as 93 ergs per gram of flesh.

Tissue dose is a physical concept and takes no account of biologic effect. In fact it takes no account of one pertinent physical effect, namely the changing efficiency of ionization according to the speed of a charged particle. The faster an ionizing particle is travelling, the more sparsely are the ions strung along its path. Thus, the heavier particles show a higher specific ionization. X-rays and gamma rays which are absorbed by producing high speed elec-

layers on small metal discs) of $UX_2$, radium D plus E ($Pb^{210}$ with "daughter" $Bi^{210}$), $Co^{60}$, $C^{14}$, and solutions of radium in several concentrations Similar standards are also sold by at least one commercial firm (Tracerlab) These cover a reasonable range of radiant spectra. The Bureau also promises to make available standards of $I^{131}$ and $P^{32}$. These being evanescent they can be used only as a check to assure oneself of the sufficiency of one's techniques in measurement.

The matter of standards has proved a thorny one. There are good reasons for questioning the millicurie values reported in published work anywhere, and clinical workers should gain some experience of their own in posology and not venture on large dosage merely on the basis of published reports.

Samples of $I^{131}$ were sent to those institutions known to be working with this isotope (61). Their measurements of the samples varied from half the average to twice the average value. A recent round of visits by Dr. Manov from the National Bureau of Standards has shown inter-agreement much improved.

Isotope shipments from Oak Ridge come precisely labeled as to millicurie content, specific activity, and chemical purity, and have proved to be fairly consistent. However, as a result of the Bureau's studies and new information (62) about the way $I^{131}$ disintegrates ("Disintegration Scheme" is the term used for this), Oak Ridge has recently had to amend its standard, and 1 mc of $I^{131}$ now is 1/1.75 as active as "1 mc." of $I^{131}$ delivered from there before 1 July 1949. This is not written in criticism of the Oak Ridge National Laboratory, but rather to show the difficulties of isotope measurement in even the most practiced hands.

## PROCUREMENT OF RADIOACTIVE ISOTOPES

The largest source of radioactive isotopes is the chain-reacting uranium pile. In this country such piles are a monopoly of the Atomic Energy Commission. The Canadians have a pile in operation at Chalk River, Ontario, and the British have two at Harwell. The French have one near Paris We don't know about U.S S R. Isotopes are also made by bombardment with nuclear particles in cyclotrons, of which there are a good many in the world. There are some useful isotopes that can be produced with the cyclotron but not with the pile, for the latter is limited to one kind of particle, viz., the neutron, to produce the nuclear reactions.

The A E.C. is using only one pile (that at Oak Ridge) to make isotopes for general distribution. By the end of 1948 they had made 4,542 shipments within the U S., and 355 to foreign countries. The product of their other piles is available only to their own National Laboratories The huge piles at Hanford are being used only for production of plutonium.

In the view of the A E.C , all use of isotopes in medicine is experimental. They are therefore delivering none to the practitioner, but only to institutions with facilities and scientific staff adequate to prosecute research and clinical investigation. They demand that use be supervised by an adequate Isotope Committee, including at least an internist, pathologist, radiologist,

ment for radioactive materials. It is ill understood by many physicians and a brief explanation is warranted here.

Marie Curie prepared a 22 mg. sample of chemically pure radium (as chloride). This is the international standard. Measurement of the activity of radium gives a half-life of 1,560 years (precise within perhaps 5 per cent). This rate of decay means that in 1 mg. of radium 37,000,000 radium atoms disintegrate every second. In any sample of radium, of course, there have accumulated radioactive "daughters," radon, RaA, etc , which are also disintegrating If these have reached equilibrium, then for each atom of one of these that disintegrates, an atom of its parent must disintegrate to replace it, and the whole family is seen to be disintegrating at the same rate When we first began to pump off radon gas and put it in tubes for clinical use ("gold seeds" are the present form), it was natural to define a unit for radon based on its activity rather than on its (very small) volume or its mass The millicurie was then defined as the amount of radon in equilibrium with one milligram of radium. In this case it happens that the radiations that we use radium for, namely, beta and gamma rays, all come from the disintegration products that accumulate in the radium with time (Ra itself giving only alpha rays), and so a millicurie of radon is clinically exactly equivalent to a milligram of radium except for its short life.

Essentially, however, it is not the radiant equivalence that is the basis of the definition, but the equivalence of disintegrations per second.

On extending the unit, millicurie, to unstable isotopes not in the radium series, one writes. One millicurie is the quantity of an isotope that disintegrates at the same rate as 1 mg of radium (i.e , 37,000,000 atomic disintegrations per second) One now discovers that one has lost all correlation with the radiant activity of radium for the various isotopes give off all kinds and energies of radiation, e.g., moderate gamma and beta from $I^{131}$, hard gamma and beta from $Na^{24}$, hard beta without gamma from $P^{32}$, weak beta without gamma from $C^{14}$ and only weak x-rays from $Fe^{55}$. Therefore one cannot measure an isotope simply by comparing the quantity of its radiation with that of a radium standard.

The basis is the number of disintegrations. Where there is a beta ray, these can be counted with a Geiger tube Efficiencies, however, vary with the energy of the beta rays, and moreover the tube is entered by only a portion of the betas produced. (This is called "geometry" in the jargon of the isotope laboratories.) Corrections for backscattering and absorption of the betas in the sample and its mounting also depend on energy Curtiss (60) gives necessary techniques

## STANDARDS

If one could have a standard sample of each isotope, then comparisons would be easy, but for short-lived isotopes the standard will not keep. One can approximate satisfaction by using a standard of some long-lived isotope, the radiant spectrum of which is similar to that of the isotope to be measured.

The National Bureau of Standards now has for sale standards (thin

cover a reasonable range of radiant spectra. The Bureau also promises to make available standards of $I^{131}$ and $P^{32}$. These being evanescent they can be used only as a check to assure oneself of the sufficiency of one's techniques in measurement.

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and physicist. In requesting allocation of any radioisotope, a statement must be made of the plan and purpose of the investigation, special instruments available for measurement and health protection (monitoring), and tools and equipment for safe storage and handling; also the education and training of the investigator(s) responsible for the prosecution of the research and the safety of personnel.

Oak Ridge production and distribution are actually by the Carbide and Carbon Chemical Corporation under contract to A.E.C. A new catalogue (63) has just appeared listing the isotopes available (fission-product or by neutron irradiation), their purity, activity, and chemical combination, with unit sizes of packages and prices per unit. Some are available "carrier-free," i.e., separated as the nearly pure nuclide with only traces of stable isotope. Such are notably $P^{32}$ (made by n, p reaction from sulphur), and $I^{131}$ (made by n, $\gamma$ reaction from tellurium, or, more recently, purified from fission products and allowed to stand long enough for the shorter-lived iodine isotopes to decay to less than 2 per cent of the total activity).

In order to further the war against cancer, the A.E.C. remits the price of isotopes used for cancer treatment or research. There remains, however, the service charge of 10 dollars for each shipment. Also, transport is a problem on account of radioactivity hazard.

Postal regulations (64) are stringent, the quantity in a package being limited to 0.1 mc. of Ra or Po; 0.13 mc. of $Sr^{89}$, $Sr^{90}$, $Ba^{140}$; 1.3 mc. of others. Radiation at the surface of the package must be less than 0.01 r in 24 hrs. Consequently most shipments are made by air express or air freight, several airlines having agreements with Oak Ridge to accept such shipments. Railway or highway freight is too slow for short-lived isotopes. If a shipment of 20 mc. of $Na^{24}$ were nine days *en route*, less than 1 $\mu$c. would remain on delivery. Pure beta emitters, like $P^{32}$ and $C^{14}$ are shipped in tin cans within a disposable shield made of cement. But gamma emitters require lead shielding, heavier the more energetic the gamma ray. Twenty mc. of $I^{131}$ comes in a glass bottle inside a lead cylinder in a wooden box for spacing, so that the radiation at the surface is less than 15 mr per hr. The total weight is about 35 lbs. $Na^{24}$ (20 mc. irradiated unit) is shipped in a 250 lb. package. The air freight is so costly that customers on the coasts find it more economical to prepare $Na^{24}$ on the cyclotron if they have access to one nearby.

Oak Ridge sells most of their product as the "pure" isotope or in a simple compound, or in the original 30 cc. aluminum can of the "irradiated unit" containing the isotope mixed with its parent.

*Tagged chemicals*.—Oak Ridge is making available an increasing number of chemicals important for tracer studies. As fast as other research organizations or commercial firms take on the production of any of these, Oak Ridge gives it up and passes on to some other needed chemicals. They are all costly, running from 100 dollars to 600 dollars a millicurie of activity for specific activities of a millicurie per millimole or so. But buying them already prepared is usually a great economy over making one's own synthesis to introduce the tracer into the desired place in the molecule.

TABLE I

Labeled Organic Compounds Available

(a) Offered by Tracerlab, 130 High Street, Boston 10, Massachusetts:

*$C^{14}$ Labeled Chemicals*

Acetylene
Alanine (carboxyl labeled)
Barium carbide ([illegible] per cent)
Benzene
Benzoic acid (carboxyl labeled)
Benzoic acid (ring labeled)
Bromoacetate (carboxyl labeled)
Ethanol (methylene labeled)
Ethyl acetate (carboxyl labeled)
Ethyl acetate (methyl labeled)
Ethyl alcohol (methyl labeled)
Ethyl iodide or bromide (methyl labeled)
Ethyl iodide (methylene labeled)
Glycine (carboxyl labeled)
Glycine (methylene labeled)
Hexaethyltetraphosphate (methylene labeled)
Methanol
Methyl iodide
Sodium acetate (carboxyl labeled)
Sodium acetate (methyl labeled)
Sodium cyanide
Toluene (ring labeled)
Tetraethylpyrophosphate (methylene labeled)
2,4-D (carboxyl labeled)

(b) Offered by the Texas Research Foundation, Box 63, Renner, Texas:

*$C^{14}$ Labeled Chemicals*

Glutamic acid (carboxyl labeled)
Potassium butyrate (carboxyl labeled)
Potassium propionate (carboxyl labeled)
Stearic acid (carboxyl labeled)
Tyrosine (labeled in beta position in side chain)

*Iodine Labeled*

2,4-D

*Sulfur Labeled*

Cysteine
Cystine
Methionine

(c) Offered by Oak Ridge (Isotopes Division A.E.C.):

*$C^{14}$ Labeled Chemicals*

Acetyl chloride (methyl or carboxyl labeled)
Alanine (labeled in 2 carbon)
p-Amino benzoic acid (carboxyl labeled)
Anthranilic acid (carboxyl labeled)
Calcium glycolate (labeled in 1 or 2 carbon)
Dried algae (Scenedesmus)
Ethyl alcohol (methylene labeled—for methyl labeled, see Tracerlab)
Ethyl iodide (methylene labeled—for methyl labeled, see Tracerlab)
Formaldehyde
Nicotinamide (carboxyl labeled)
Nicotinic acid (carboxyl labeled)
Sodium formate
Sodium propionate (labeled in 1 or 2 carbon)
Urea

(d) Offered by Abbott Laboratories, North Chicago, Illinois:

Diiodofluorescein (iodine labeled)
Gold, colloidal

The Fifth Semiannual Report of the A.E.C. (Superintendent of Documents, Washington 25, D.C., price 45 cents) lists more compounds of $C^{14}$ and a few of $S^{35}$, $P^{32}$, $Zn^{65}$, $Co^{60}$ and $Au^{198}$, available or soon to be available, without naming the supplier. For isotopes produced by other agencies (cyclotron), the A.E.C. claims no jurisdiction. But one must obtain an A.E.C.

allocation before purchase of a labeled compound from any supplier if that supplier obtained his radioisotope from Oak Ridge.

## RADIATION HYGIENE

Radiologists and radium workers have long been aware of the peculiar hazards they are exposed to. Codes (65, 66) for radiological safety have been promulgated by the National Bureau of Standards (*vide infra*) and by the American Standards Association.

The wide expansion of use of radioisotopes and the development of radiating machines of varied type and extraordinary power (cyclotrons, synchrotrons, betatrons, megavolt x-ray machines, chain reacting piles and, perhaps soon, nuclear reactors for industrial and transport power) have greatly increased the variety and amount of radiation hazard. Within the Manhattan District was developed a specialty called Health Physics. Health Physicists were physicists with the special duty of devising means of detection of radiation hazard and of protecting personnel from damage by radiation. In consultation with the physicians, especially the radiologists, they set up "tolerance limits" and promulgated working safety rules. In hazardous departments, i.e., the piles at Chicago, Oak Ridge, and Hanford and their associated chemical and physical and biological laboratories, the Health Physics Departments provided "monitors" trained in the use of radiation detection instruments (also called "monitors") to guard the employees' health. Noteworthy were continuously operated detectors to reveal dangerous levels of radiation in a working area, air filters to measure atmospheric pollution, ionization chambers, and photographic film packets (called "film badges") worn by personnel, hand and foot "monitors" to detect radioactive soiling of hands and shoes, and portable instruments to measure the degree of contamination residual after accidental spilling (or explosion) of radioactive material.

The Health Physics Departments also carried on biologic research to try to establish degrees of hazard carried by radiation and norms of protection pertinent to the less familiar kinds of radiation being dealt with, i.e., beta rays, neutrons (fast and slow), and the radioactive materials (fission products) from the piles which could get into the body and irradiate it from within.

There were also new problems in chemical toxicology, e.g., uranium, fluorine, beryllium, which, not being radiant, will be passed over here, except to note a new industrial disease, beryllium pneumonia (67, 68) appearing in the fluorescent lamp industry.

*Codes*—For a couple of years a self-appointed National Committee on [illegible]

medical fields where hazard appears likely, and to this end have set up several subcommittees. The one on x-rays has revised the code (66) on medical uses up to two million volts. The Code for radioactive isotopes, of

especial interest to all radiobiological laboratories, and containing instructions for safe disposal of radioactive wastes, will be issued by the time this is printed (69) The subcommittee on "permissible dose" has reached tentative agreement to lower the former U.S. "tolerance dose" from 0.1 r per day to 0 3 r per week and to change the word from "tolerance" to "permissible," on the plea that no dose can be named that is tolerated without some presumptive harmful effect, however difficult to demonstrate

The Council on Physical Medicine of the A.M.A. has taken cognizance of the new hazard and has sponsored a report summarizing the hazards of radioactive isotopes (70). The types and energy of radiation from the various isotopes and the solubilities and absorption and retention of their compounds are so different, and the situation of the persons exposed so diverse, that only a complicated table can summarize the situation.

## THE ATOMIC BOMB

Much of the data concerning the A bomb is secret. Nevertheless much has been written in speculation about the engineering of it. This will be passed over here. Eight A bombs have been shot off. Medical and biological observations were made after Hiroshima and Nagasaki, and animal experiments were carried out at Bikini

Physicians have to face the possibility that they will be called upon to alleviate the wounds in military and civil populations caused by an A bomb (71, 72) The military establishment has issued a series on "What Every Military Officer Should Know" about the A bomb (73) The result at Hiroshima was described in a very able manner by Hersey (74), with considerable emotional effect. It is not too late to read it—or reread it. DeCoursey (75) gives the pathologic anatomy of those dying early and up to four months after the blast.

From an air burst, ordinary radiation (heat burns), the blast wave, and flying fragments of wood and glass, together with secondary injuries from the fire that follows, account for most of the deaths. Only about 15 per cent of deaths are the result of the gamma rays and neutron rays that come in such enormous amount at the time of explosion (76). Their intensity falls off with distance (as the square of the distance), but also they are absorbed by air A mile of air forms an absorbing layer equivalent in mass to a 6 ft layer of water. This might be about 20 half-value layers for these gamma rays, which would therefore penetrate in the amount of only $(\frac{1}{2})^{20}$, or about one part per million Neutron rays are pretty well slowed down and absorbed (by nuclear reactions) in a few hundred yards of air. Few neutrons reached the ground at Hiroshima and Nagasaki so that induced radioactivity was negligible, and the radioactive smoke was swept up into the stratosphere, with very little subsequent fall-out. The ruined city was therefore essentially no radioactive hazard.

treatment. For burns and physical trauma we know how to determine prognosis, how to choose the ones who may yet be saved. For radiation injury however, physicians lack clinical experience, and even the experts are impeded by the long latent period and by a lack of dependable information on the quantitative effects of total-body irradiation in man. Survey of opinion as to lethal and incapacitating total-body doses revealed a discouraging variability of presumed "expert" opinion (77). It seems likely that physicians will be very inefficient at picking out the group of victims whose radiation injuries warrant an attempt at therapy. This will be true whether they are chosen on the basis of symptoms (nausea, diarrhea, hemmorrhage, etc.) or of measured or estimated dose of radiation sustained. Report of opalescence in blood serum of irradiated animals as a bad prognostic sign has not yet been confirmed (78). The group chosen as "borderline" will actually comprise a large number who are already doomed and another large number who would recover without therapy.

*Treatment.*—Many researches are reported concerning drugs, etc. that alleviate radiation injury. Antihistaminic drugs relieve nausea in clinical radiation therapy, but in guinea pigs have been reported to increase lethality of total body irradiation (79). Desoxycorticosterone (80) may help, and so may pyridoxine (81). Protamine and toluidine blue (82) and also rutin (83) are antidotes to heparin and have shown a beneficent effect in total body irradiations of some mammals, but rutin was disappointing in rats (84) and mice (85). Folic acid is also disappointing (86). A flavonoid (vitamin P) from lemons reduced irradiation mortality in guinea pigs by half (87). Transfusions may tide a borderline case over an otherwise fatal period of absent hematopoiesis, but they do not restore platelets even temporarily (88). Exercise to exhaustion increased the death rate of irradiated rats (89).

On the whole the good results reported are so modest and so little likely to affect the outcome, except in an extremely narrow range of "critical

available physicians "swamped."

In the case of a city sprayed with fission products from an A bomb burst in a neighboring harbor, the heat and blast injuries will be fewer, but the problems of hygiene posed by the radioactive contamination may prove enormous (90). Necessary exodus from radiant areas and consequent panic (76), especially in the face of a lethal "miasm" that cannot be seen, felt, or smelt, will multiply also the problems of conventional hygiene and public health. Some of these things are dealt with in the Report of the Commission on Civilian Defense (72). If physicians foresee that they are likely to have to answer questions of the populace in regard to radiation hazard and safe and dangerous areas, they will at present have to make their own preparations in knowledge and equipment. Average expert opinion is that 100 r of gamma exposure (total) in a few hours or a few days is not lethal. The beta and alpha

activity of fission products makes them dangerous if they get into food or water, or are inhaled as dust. Presumably water and food control would be taken over promptly by those experienced in radioactive measurements. Civilian Defense has not yet announced its choice and design of an instrument to detect and measure radiation. A number of Geiger Counters have been put on the market (91) for uranium prospecting or for demonstration, etc.

### Genetic Effects of Radiation

The A bomb has focussed attention on the possibility of injury to the race by radiation. The genetic mechanism of cells is definitely vulnerable A dose of 5 r stops half the mitoses in a mouse's epidermis (92). Larger doses break chromosomes. Genetic injuries increase linearly with total dose and without recovery between exposures (93). Different authors, working with different materials, vary in their estimates of the magnitude of the hazard. Examples are 0.2 to 1.0 per cent genetic injuries per 100 r. Some have become quite frightened by the prospect (94). Quantitative estimates make it seem possible that the race will survive, however (95).

Most mutations are lethal, and most of the nonlethal ones are deleterious. Experiments with a mould have beautifully demonstrated rare beneficial mutations induced by irradiation (96). They are demonstrable because they are reversions from a state of narrowed food-dependence induced by a previous irradiation.

Radiation-induced mutations have been used in plant breeding, occassionally with good effect. Important for medicine are improved strains of mould to produce penicillin and streptomycin (97). The chances of success are small. Only 3 out of 3,700 superior mutants of streptomyces proved stable.

Some authors think the mutagenic effects of the several agents (x-rays, ultraviolet, neutrons, mustard gas) are different (97).

## EDUCATION

The enormously rapid expansion of nuclear science and activities has made the dearth of trained scientists pretty acute The several facilities of the A.E C have their biological laboratories in which graduate education is fostered among their own staffs by seminars and domestic scientific meetings ("information meetings") The most important of these are in the great National Laboratories of Argonne, Oak Ridge and Brookhaven. University ideals operate very directly.

### The National Laboratories

Argonne is run for the A E.C. by the University of Chicago, and 31 universities, colleges and research institutes of the midwest are formally associated as participating institutions. Participation in the scientific work is open also to others without such formal association.

Oak Ridge is operated by a corporation, but now has attached to it the Oak Ridge Institute of Nuclear Studies which is operated by 24 universities

of the south under contract to the A.E.C. In the first six months it gave intensive four week courses in research uses of tracers to nearly 100 biologists and medical scientists coming from more than half the States. These courses were being continued into 1949, three being scheduled for the first quarter.

Brookhaven is operated by Associated Universities under contract to the A.E.C. This is a co-operative of nine eastern universities. Brookhaven has held several meetings open to interested scientists, which have served a high level educational purpose One of these produced a report which temporarily served as a text book on radioiodine.

The University of California operates Los Alamos, which is avowedly military in purpose, and whose small but active biological divisions seem less accessible than the others. At Berkeley their Radiation Laboratory and Crocker and Donner Laboratories are under contract to the A.E.C, the last two being for biological and medical science. They have already given three intensive Summer courses of one or two weeks at their medical schools, two in San Francisco and one in Los Angeles.

Hanford is just for plutonium production, and Ames, Knolls and the Atomic Power Division of Westinghouse are industrial in purpose. These laboratories have biology and health physics departments, but give no public instruction. The National Military Establishment and U.S Public Health Services have radiobiology laboratories, notably at Bethesda, at Randolph Field, and at Hunters Point (San Francisco). The latter uses old "target ships" from Bikini for training Navy personnel in radiological safety. The Veterans Administration has a successful program for developing radioisotope laboratories in the major Veterans Hospitals, which are of course now linked to medical schools

The A.E.C. has given a course in radiobiology in Washington. This was repeated a half dozen times in order to accommodate the large number of applicants

## THE GROWTH OF RADIOBIOLOGY

Radiobiology was once a small matter, pursued by a few general biologists, physiologists, pathologists, and clinical therapists using x-rays and radium. Since the revolution produced by nuclear physics—really since the invention of the cyclotron—the subject has expanded with the new radioactive tools thus made available. Further acceleration has come since Hiroshima, the Smyth Report (99) explaining it, and the release of more and more data accumulated in the secret workings of the Manhattan District The growth has been almost prodigious since the Atomic Energy Commission began to supply radioactive isotopes from the chain reacting uranium pile at Oak Ridge. With all these developments, one sees that radio-
biological science and
upon the science and t
the radiobiologist is nc...
this field find the necessary physics hard to learn. Physicists carrying their radioactive experiments into the biological and medical fields perhaps find

the necessary life science even more difficult, and especially the peculiar understanding and intuitions that are a tacit but essential part of the trained physician. Nevertheless there are a number of outstanding examples of successful physicists-become-biologists, especially in the field of health physics (radiation hygiene), and of physicians-become-physicists. In this growth of a science, books are a necessity, and some of these are listed in the literature cited (98 to 114).

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# DISEASES OF THE EAR, NOSE, AND THROAT[1]

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## Introduction

Adequate training in general surgery is essential before beginning training in the surgery of a specialty. If, in addition, the young doctor is exposed to the discipline of research during his training period he will make a better and more intelligent surgeon than one who is merely a good surgical technician. Surgical operation is no longer the panacea it was 10 years ago, and the idea of prevention and search for the primary causes of disease should be a part of the daily experience of every good surgeon.

## Chemotherapy

Marshall (1) reviews the evidence bearing on penicillin dosage schedules and concludes that the maintenance of a more or less constant blood concentration is not necessary for efficient therapy. The extremely ill patient is an exception, but in the vast majority of patients with pneumococcus pneumonia or other conditions for which penicillin is given, one or two injections of aqueous penicillin per day is adequate Such a schedule has obvious advantages, the chief of which is an opportunity for the body to build up its own defenses. For nearly two years we have given from 600,000 to 1,000,000 units of penicillin G once a day to otolaryngological cases with success.

During a single decade the indications for sinus and mastoid surgery have become greatly modified by the demonstrated ability of the sulfonamides and antibiotics to control acute infections, or at least modify them to such an extent that surgical measures are either avoided or limited to more simple procedures. The sulfonamides have decreased in popularity because of the large amounts that must be taken by mouth to insure full therapeutic effect and because of the incidence of skin rash, drug fever, crystalluria, and renal complications. Hiehle (2) discusses the efforts to avoid these complications by giving a combination of sulfonamides rather than massive doses of any one sulfonamide. The rationale of sulfonamide mixture therapy developed from the experimental demonstration that to a saturated aqueous solution of one sulfonamide, two or three other sulfonamides could be added Each of the components is as soluble in the mixture as though present in the solution alone. Thus, if the solubility of sulfadiazine in water is 7 mg per cent, the solubility of sulfathiazole when added to the sulfadiazine solution is 34 mg. per cent and sulfamerazine 20 mg per cent, making the

[1] This review covers the period from approximately 1938 to 1948.

combined soluble sulfonamide mixture 61 mg. per cent. Double and triple combinations of sulfonamides when given by mouth are far less toxic, the blood levels are higher, and the incidence of crystalluria is negligible. It was found that a combination of sulfadiazine and sulfamerazine prevented crystalluria as effectively as the administration of 12 gm. of sodium bicarbonate daily with either sulfadiazine or sulfamerazine alone in full dosage.

The antibiotics, however, have not entirely displaced the sulfonamides. In the treatment of some infections the two types supplement each other. According to Schenck (3), antibiotics are of no value in uncomplicated allergy of the respiratory passages but are very effective against secondary infections and in forestalling bacterial sensitization. Because allergic patients are prone to become sensitive to the antibiotic drugs, especially when they are administered over a long period of time, their use for the prevention of secondary infections is not justified. Infected allergic tissues are less amenable to chemotherapy than is a similar infection in a nonallergic individual. Chronic infection of sinuses with irreversible allergic changes in the lining mucous membrane demands some form of surgery in addition to chemotherapy.

It is poor therapeutic practice to give antibiotics for mild and transient sinus infection because prompt control of the infection impedes immunological responses. As a result, there are frequent recurrences which are also treated with chemotherapy because of the success attending its use during the first attack. Repetition of courses of chemotherapy not only fails to prevent the gradual development of irreversible changes in the mucous membrane lining the sinuses, but fosters resistant strains of bacteria and may sensitize the patient to the drug. Chronic sinus infections are resistant to antibiotic therapy because the drug cannot penetrate the abnormal tissues resulting from repeated or prolonged infection. Tyrothricin is insoluble in water, does not penetrate tissue, and is of no value in the local treatment of chronic sinusitis. Irrigation of the wound with tyrothricin at the conclusion of an operation, however, kills all susceptible organisms on the exposed bone and soft tissues, helps to prevent postoperative wound infection, and greatly simplifies and reduces the number of postoperative treatments.

## Mechanism of Virus and Pyogenic Infections of the Upper Air Passages

Proctor and his associates (4) again emphasize the importance of maintaining normal ciliary activity. Nasal medication is the commonest source of ciliary trauma. The drugs least harmful in nasal medication are neosynephrine 0.25 per cent, ephedrine 1 per cent, and penicillin 1,000 units per cc. In any nasal medication, the first question should be the possible toxic effect of the drug on cilia.

Proctor *et al.* (4) also point out that the most vulnerable area in the upper respiratory tract is the lymphoid tissue in the nasopharynx This observation leads to a discussion of the common cold, which is the underlying cause of lymphoid hyperplasia, auditory tube obstruction, certain types of impaired

hearing, and practically all pyogenic infections of the ear. In addition, hyperplastic lymphoid tissue may appear in the choanae where it is inaccessible to surgical removal and, in children particularly, is a cause of recurring colds with nasal obstruction and sinus infection. The mucous membrane of the sinuses and ears has a remarkable capacity to recover from one or a series of acute infections. The antibiotics or sulfonamides may promptly control the acute manifestations, but they do not remove lymphoid tissue or protect against recurring infections. To prevent chronic infection of the ears or sinuses the otolaryngologist should search for and correct all conditions that contribute to recurring acute infections, especially allergy. Also nodules of lymphoid tissue on the posterior part of the septum and near the posterior end of the middle turbinate, even though they look small and insignificant, should be removed either by surgery, irradiation, or both.

Kruse (5), in 1914, showed that the common cold is due to a virus infection. Dochez and his associates (6) were the first in this country to confirm this finding, and what we know about the common cold today is due in large part to the years of work of these investigators. The common cold virus, in common with all other viruses, grows only in living tissue. It can be cultivated by inoculating tissue cultures or chick embyros. Symptoms of the common cold usually manifest themselves from 24 to 48 hr. after intranasal inoculation with the virus, both in chimpanzees and in human volunteers. The first subjective symptoms complained of by the volunteers are a "hot spot" in the nasopharynx, nasal obstruction, sneezing, and abundant mucous discharge. Virus infection never causes a purulent discharge, which is always due to secondary pyogenic infection. The virus must enter a living cell before it can multiply and cause clinical symptoms and it must be in undisturbed contact with the cell for at least 30 min. before it gains entrance. The virus infection, together with the hyperemia, edema, and increased secretion of thick mucus, seems to promote and foster pyogenic infection of the ears, sinuses, and other parts of the respiratory tract. All evidence suggests that the bacteria of the upper respiratory tract are powerless to initiate infection (7, 8).

The primary object of investigators of the common cold has been to find a vaccine or some measure that will prevent colds, but so far all efforts in this direction have been a failure. Antibiotics and sulfonamides control the acute bacterial complications of the common cold, but they have no effect on the virus and will not prevent recurrences. In what part of the upper respiratory tract does the virus find a lodging place where it is undisturbed for a sufficient length of time to allow it to enter cells and begin to multiply? Why are some children and some adults more susceptible to colds than others? The explanation must be largely mechanical. Clinical observations suggest

*It has been repeatedly observed that children may be comparatively free of*

colds and ear or sinus infections for a year or more following removal of their tonsils and adenoids or adenoids alone. When these children again begin to have symptoms of colds, examination with a nasopharyngoscope usually shows a condition in the nasopharynx similar to the granular condition so frequently seen in the pharynx after this operation. These nodules contain crypts, and evidence that these crypts are serving as a portal of entry for the virus is furnished by the marked decrease in the number and severity of colds that follows a course of treatments with the 0.3 mm. monel metal 50 mg. nasopharyngeal radium applicator. In the dosage employed, irradiation stops mitosis and the formation of new lymphocytes to replace those constantly being lost by the normal dissolution process, thus causing hyperplastic nodules of lymphoid tissue gradually to shrink and disappear, obliterating crypts, and leaving in their place smooth, normal looking mucous membrane and no favorable places for the virus to lodge and grow in the nasopharynx.

It is impossible to free permanently the upper air passages of bacteria. But if these bacteria are relatively harmless until activated by virus infection and if the principal area in which the virus lodges and begins to grow is the nasopharynx, it is obvious that in order to lessen or obviate virus infections we must supplement drug treatment of the acute condition by removal of crypts and crevices in nasopharyngeal lymphoid tissue with a combination of operation and irradiation. It is neither safe nor necessary to use irradiation in sufficient dosage to remove permanently all lymphoid tissue in the nasopharynx. Moderate irradiation in conjunction with operation is a therapeutic measure that temporarily relieves symptoms. Used in this way, it is a simple and safe measure, but does not permanently prevent a recurrence of symptoms. Therefore, every patient should be followed and examined by the otolaryngologist at least once a year, just as the dentist has his patients return at regular intervals for examination and whatever treatment may be indicated. Irradiation of the nasopharynx is no panacea, but in both children and adults it is an invaluable therapeutic measure.

Murphy & Sturm (9) review the literature on lymphoid tissue and antibody formation and find from their own experiments that animals with hypertrophied lymphoid systems have an enhanced ability to produce antibodies. The production of antibodies and the hypertrophy of lymphoid tissue in adrenalectomized animals is far in excess of that produced in normal animals. The authors confirm the observation that release of antibodies may be augmented by the injection of adrenal cortical hormones, but conclude from their experiments that the hormone is not essential for this release and therefore antibody production is not entirely under the control of the adrenals. At any rate, there is growing evidence that lymphoid tissue in the upper air passages has an important function and that it should never be ruthlessly destroyed with operation, electrocoagulation or irradiation.

### Irradiation of the Sinuses and Nasopharynx

Laing (10) discusses roentgen treatment of sinusitis. He has treated more than 4,000 children, the majority being between four and seven years of age.

None had a history of allergy and nasal smears were negative for evidence of allergy. Films showed varying degrees of ethmoidal and maxillary sinus infection in these children, but neither sulfonamides nor antibiotics ever entirely cured the condition. Recurrences at intervals of six to eight weeks were common. The sinuses were treated with x-ray, and if cough was a prominent symptom the lung roots were also treated. Of 900 children, 639 were clinically free of evidence of sinus disease for at least one year. We suspect that the favorable results in these cases are due to irradiation of nasopharyngeal lymphoid tissue and less frequent infections, rather than any direct effect on the mucous membrane lining the sinuses. The important question is whether the irradiation should be administered in a series of roentgen ray treatments, which must affect to some degree the salivary glands and the centers of ossification in the face and cervical vertebrae, or be applied directly to the nasopharynx with a beta ray radium applicator. We have obtained equally good results in lessening the frequency and severity of colds and complicating sinus infections by irradiating the nasopharynx alone. It is now possible, with a combination of antibacterial drugs and a better understanding of the etiology of sinus infections, otitis media, and certain types of hearing impairment, to diagnose and correct the underlying cause of these maladies during childhood, before irreversible changes have occurred in the mucous membrane of the sinuses and middle ears. All studies aimed at the prevention of chronic, disabling ear and sinus disorders later in life should be encouraged and welcomed by the medical profession.

## Carcinoma of the Upper Air Passages and Esophagus

Morton (11) describes cancer as a purposeless growth of cells that steal and trap the nutrients necessary to survival of the host. Repair of tissue is an orderly process. Each cell carries out its function with precision. Why cells in a healing wound reach a certain stage in growth and then stop is a mystery. The problem in cancer is what has gone awry inside the cells. Growing cells can be made to undergo cancerous change by prolonged and unremitting irritation or injury that damages but does not destroy the cell When a sufficient number of stimuli have been given to cells, a profound change takes place in cellular behavior. No additional irritation is necessary. The inciting agent may be withdrawn, but the change within the cells has become fixed and they proceed to develop in an abnormal fashion The inciting factors set off an intracellular mechanism which is self perpetuating and permanent. Some malignant tumors appear to be under the control of normal enzyme systems, as illustrated by the effect of castration or estrogens on cancer of the prostate.

From the available evidence, it must be concluded that some viruses are inciting agents, but they do not differ essentially from any other chemical, physical, or biologic incitor except in rapidity of action. A cell-free filtrate will produce sarcomas in chickens, and filter-passings agents will produce tumors in frogs, rabbits, and mice It is difficult to assume however, that viruses are present in many tissues of the body and remain dormant until

some inciting factor calls on them to initiate the malignant change. In many malignant growths, no virus can be demonstrated. The border line between normal and abnormal growth is hard to define, and the diagnosis of cancer should never be made without confirmatory histologic evidence.

In an interesting discussion of cancer of the head and neck, Martin (12) states that chronic irritation is an important contributing factor, but the form of the irritant is less important than its chronicity. Chronic glossitis and stomatitis, due to avitaminosis, excessive smoking, leucoplakia, broken teeth, or ill-fitting dentures are statistically important causative factors, and point a way toward prevention of malignant growths in the mouth. About 90 per cent of cancer of the mouth is epidermoid carcinoma. The more malignant, less differentiated varieties of carcinoma are usually located in the posterior part of the oral cavity—the tonsil and base of the tongue. In this location, the primary lesion rarely produces any symptoms in its early stages.

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In males with cancer of the tongue, about one in every three patients will be found to have a positive seriologic test for syphilis. If the examining physician suspects cancer, he should always take a specimen for biopsy. Cancer of the mouth is among the more favorable varieties of malignant neoplastic disease from the standpoint of treatment and cure. Prognosis depends on early diagnosis and prompt treatment with surgical excision, roentgen radiation, or radium therapy, either alone or in combination. The five year cure-rate is most favorable for the lip and least favorable for the tonsil and gums.

Cancer of the nasopharynx, more than any other malignant tumor in the head and neck, is seen in children and young adults. It is also one of the most malignant growths of the upper respiratory and alimentary tracts. The first manifestation of a primary growth in the nasopharynx may be metastasis to cervical lymph nodes, occlusion of the auditory tube, and impaired hearing, otitis media, or diplopia due to involvement of the sixth cranial nerve. Surgical removal of a malignant tumor in the nasopharynx is not possible. In contrast with growths of the mouth and larynx, cervical metastasis in nasopharyngeal cancer does not appreciably alter the prognosis, since the growth is often anaplastic and highly radiosensitive.

From the standpoint of early symptoms, cancer of the pharyngeal wall is one of the more deceptive neoplasms occurring in the head and neck. At times the complaint referred to this region may be so vague and indefinite that the history resembles that of globus hystericus or anxiety neurosis. Chemotherapy, antibiotics, blood transfusion, and new techniques of anesthesia have made it possible to extend the range of surgery to include many of these malignant growths in the pharynx.

There are only three important symptoms in cancer of the larynx:

hoarseness when the growth arises on the vocal cord, pain and discomfort on swallowing, often referred to the ear, and cervical metastasis. It is important to emphasize and publicize the fact that persistent hoarseness for more than two weeks is always serious, and it is imperative to find the cause. A differential diagnosis on clinical characteristics alone is often inaccurate. Histologic examination of a biopsy specimen in this area also is essential to a diagnosis. When a diagnosis of cancer has been made and a method of treatment is proposed that would deprive the patient of speech, the natural reaction is one of reluctance and resistance. Fractional radiation therapy has been used for *twenty years, but the early hopes of a cure by this method have not been*

cartilage is involved. If the growth is limited to the interior of the larynx, an equally high percentage is cured with total laryngectomy.

Scholl & Ayash (78) find a disappointingly small percentage of five year cures among 246 patients treated with deep roentgen ray therapy for cancer of the larynx. Previous to 1940, the routine procedure was to give 5,000 r over a period of two or three months, but since that date the dosage has been increased to 6,000 or 7,000 r in a little less than one month. Of 104 patients treated with the heavy dosage, only five were alive at the end of the five year period of observation If adequate radiation fails to produce an evident decrease in the size of the growth, subsequent treatment, even though it is more intense, is of little or no avail. If the growth decreases in size or ap*parently disappears under treatment, it does not always mean a cure.*

Malignant lymphoma of the cervical nodes is due to either lymphosarcoma or Hodgkin's disease. Lymphosarcoma is radiosensitive, and in most cases the initial response is good The five year cure-rate is 52 per cent, but to obtain a cure the dosage must be maximal for lymphosarcoma, as it is for epidermoid cancer. Moderate irradiation may destroy half or more of the cells in a malignant growth, but to destroy every cell may require four or five times the amount of radiation.

Experience in cancer clinics has shown that the overwhelming majority of malignant tumors in the neck are metastatic from a silent primary neoplasm somewhere in the mouth or upper air passsages. It is a question whether a malignant growth ever arises in the vestigial remnants of the bronchial apparatus Also cancer of the carotid body is one of the rarest of the malignant tumors of the neck Most tumors of the salivary glands, even when malignant, tend to be noninvasive As a rule they are not radiosensitive and the only effective method of treatment is surgical.

Tumors originating in the ethmoidal sinuses usually grow downward into the nasal cavity and antrum, laterally into the orbit, or backward into the sphenoidal sinus. Malignant growth in the frontal sinuses is rare. As

with most forms of cancer in the upper respiratory and alimentary tracts, the predominant variety found in the paranasal sinuses is squamous carcinoma. Swelling of the cheek, floor of the orbit, or bridge of the nose is the common initial symptom in cancer of the paranasal sinuses. The next most frequent symptoms are nasal obstruction and a bloody discharge from the nose. Metastasis seldom becomes an important clinical problem. Radiation therapy has been widely employed for many years in the treatment of cancer of the nasal sinuses, but the results have been disappointing. Cancer-lethal doses of irradiation in this region frequently produce serious complications, such as destruction of bone, osteomyelitis, and often hemorrhages. These and other complications of cancer-lethal radiation almost always call for radical surgery. The chances of making an early diagnosis are poor, since early cancer in this area is silent in its symptoms in contrast to growths on the lip, anterior portion of the tongue, and vocal cords.

Every otolaryngologist should read the articles of Lahey (13) on tumors of the neck and Wookey (14) on the post-mortem findings in a large group of cases with cancer of the hypopharynx or esophagus. Malignancy is not rare in neck tumors, and it is important to determine with biopsy the character and point of origin as early as possible. This is particularly true of lymphomas, since Lahey reports a five year cure of 29 per cent of 181 patients with roentgen ray treatment. Of the midline tumors and cysts, the rarest is the lingual thyroid and the commonest is the thyroglossal cyst. The fetal thyroglossal duct extends from the isthmus of the thyroid to the foramen cecum on the back of the tongue, but thyroglossal cysts are usually located a little to the left of the midline of the neck at the level of the notch in the thyroid cartilage. These cysts usually appear during childhood, but can delay their appearance until adult life To avoid recurrences the cyst, together with the central section of the hyoid bone and any continuation of the thyroglossal duct must be followed up to the base of the tongue and removed.

Carotid body tumors and branchial cysts are frequently located at the same level and must be differentiated. The course of the branchial sinus from which the cyst arises is extremely superficial from a point just in front of the sternomastoid until it dips beneath the digastric muscle to enter the pharynx at the region of the tonsil. Branchial cysts are movable and enlarge outward in contradistinction to carotid body tumors, which are fixed and enlarged inward and upward toward the base of the skull. Often they bulge into the pharynx to such a degree that they interfere with swallowing. Lateral aberrant thyroid tissue can occur as a chain of small glands under the sternomastoid or as a single discrete tumor, and must be differentiated from tuberculous glands, lymphosarcoma, and Hodgkin's disease The final diagnosis however, can be made only by removal of a node and histologic examination.

Intrathoracic goiter is the commonest of the low-lying tumors of the neck, but must be differentiated from fibroma of the esophagus. Both ascend and decend with swallowing. Deviation of the trachea due to goiter may be

demonstrated with x-ray, and the outline of the fibroma and distortion of the esophagus can frequently be shown with a swallow of barium sulphate. Other low-lying tumors are: a fixed firm mass extending above the clavicle, which may be the first evidence of carcinoma in the upper lobe of the lung, and tumors of *Virchow's gland, which is located behind the insertion of* the left sternomastoid and when enlarged indicates extension of carcinoma of the stomach through the thoracic duct.

Wookey (14) gives the postmortem findings in 70 cases with cancer of the hypopharynx or esophagus. The growth was in the hypopharynx or upper end of the esophagus in 25 per cent, in the middle portion in 45 per cent, and at the lower end in 30 per cent. The tumors were epidermoid in all but three cases. Two of these were adenocarcinoma and one was a basal cell growth. In cases with a keratinizing carcinoma, metastases were found in 61 per cent. In an equal number with an anaplastic growth, metastases were found in 92 per cent Cancer of the esophagus was found four times as frequently in males as in females. Cancer in the retrocricoid region is almost entirely confined to women. In patients with a midesophageal cancer, a paralyzed vocal cord usually means involvement of the superior mediastinal lymph nodes.

Guild (15), in 1941, reported a hitherto unrecognized structure in normal human temporal bones, which he called glomus jugularis. It consists of clumps of cells similar in appearance to carotid body cells, which are located in the adventitia of the dome of the jugular bulb They are very vascular and have since been shown to give rise to tumors which fill the middle ear, often paralyze the face, and by pressure destroy the cochlea. They have *heretofore been called angioma or angiosarcoma.*

## The Ear

*Deafness.*—Our knowledge and interest in the ear and its central connections has been greatly increased and broadened during the past two decades. The text books of only a few years ago described in great detail the symptoms, complications, and surgical treatment of infections, but had little to say about other cases of hearing impairment. This change is due in part to the advent of the audiometer, to the almost complete elimination of chronic ear infections by the sulfonamides and antibiotics, and to the nasopharyngoscope and other improved methods of diagnosis. The more we correlate audiograms, tuning fork, and speech-hearing tests with the pathologic lesion that is the cause of the hearing impairment, the more evident it becomes that *expert examination and treatment of school children* is essential if the incidence of impaired hearing in our adult population is to be decreased. Every type of hearing impairment seen in adults can be found in children (16 to 20). Some are reversible provided the etiologic factors are recognized and eliminated before secondary changes in the middle ear have permanently interfered with movement of the ossicular chain. It is hoped that early recognition and treatment of hearing disorders of all school children will ulti-

mately be made possible as a public health measure. One move in this direction was the establishment of pilot clinics in several of the counties of Maryland to determine the efficacy of nasopharyngeal radiation, supplemented when necessary by chemotherapy or surgical removal of tonsils and adenoids (4). Radium treatment of nodules of lymphoid tissue in and around the pharyngeal orifice of the Eustachian tubes has also proved to be a valuable addition to the standard measures used in the treatment of hearing impairment following recurrent attacks of otitis media (16, 21). During World War II the same type of radium treatment was used by the Army Air Force to prevent recurring attacks of aerotitis among its personnel (22 to 27). Asthma and asthmatic bronchitis due to bacterial sensitization, especially in children, has been treated successfully with radium alone or in conjunction with antibiotics, since it is so frequently due to chronic or repeated nasopharyngeal infections. However, here as in other maladies, radium treatment must not be used except after the most careful evaluation of the history and physical findings (28, 29).

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fied with adequate controls. Another publication reports improvement in both the perceptive and conductive type of hearing impairment, including otosclerosis, following injections of vitamin A (31). It is reasonable to expect improvement with this treatment if the hearing impairment is recognized in its earliest stages and is shown to be due to vitamin A deficiency, but it does not seem likely that cases of advanced impairment could respond favorably, considering the findings of Melanby (32), Loch (33), and Perlman (34) Marked improven [illegible]
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Pohlman (36) reports that a marked improvement in hearing may be obtained in some patients by placing an acoustic probe against the round or oval window, or the fenestrum in the semicircular canal. Ruedi & Furrer (37) discuss the experimental and clinical aspect of acoustic trauma in industry and war. They have devised an ear defender that withstood experimental test, but from the description we suspect it is too large and cumbersome to be practical for the soldier or the factory worker

For thousands of years the child and even the adult with impaired hearing has been thought to be mentally deficient The child with normal hearing spends years learning to talk. He imitates what he hears, and except through long and painstaking education, no child without hearing has ever learned to talk normally. Since 1943, a new branch of knowledge called audiology, the science of hearing, has come into being. This has given new impetus to work with children who have impaired hearing. It is no coincidence that every carefully executed hearing survey of school children selects about one

fifth of the group for further examination. Correlation of hearing tests with the school record shows that the majority of this selected group are among the inattentive, the slow, the difficult, the classroom problem children. This is direct evidence that even a moderate hearing impairment, which often escapes the notice of parents and teachers, involves the entire psychosocial pattern of the child. Approximately five per cent of all school children have hearing impairment severe enough to interfere with general behavior and progress in school.

The recognition of impaired hearing in the child of preschool age however, is even more important As far as language is concerned, the child of three or four is a highly geared learning mechanism. It is, therefore, important that at this age his hearing impairment should be recognized. A method for the determination of the tone auditory threshold in young children through changes in galvanic skin resistance in response to auditory stimuli has been described by Bordley, Hardy & Richter (46). This test differs from the galvanic skin resistance response described by Michels & Randt (47) and Doerfler (48) in that a conditioned response is obtained by following the pure tone test signal with a faradic shock. A continuous record is taken of the skin resistance. Each time a tone is sounded, there is a sudden shift in the skin resistance, apparently as a result of the psychological anticipation associated with the expected shock. Thresholds obtained by this method, when a person with normal hearing is tested, agree almost perfectly with the audiogram. It is obvious that this method will also be useful in demonstrating malingering and in the study of patients with a psychogenic hearing impairment. A comprehensive and interesting survey of the field of audiology is presented in a book edited by Davis (49), which presents very clearly the problems of training and rehabilitation of the deaf. Many of the techniques developed in the Armed Services have been carried over to civilian practice, and clinics are being set up in university medical centers for training in speech-reading and the fitting of hearing aids (50 to 59).

*Fenestration operation.*—One of the great problems in the surgical treatment of otosclerotic deafness has been closure of the fenestrum. Lempert's conclusion (60) that bone is one of the major causes of closure of the window has been verified by Lindsay (61) Among the efforts to prevent closure have been the placing of the fenestrum in an elevated part of the operative field, extensive removal of the periosteal layer of bone around the fenestrum, and the use of a microscope and constant irrigation (62) The most recent suggestion, proposed independently by House (63), Lempert (64), and Loch (65), is to use the burr until the bone overlying the perilymphatic space has been reduced to a thin layer, clean the area of bone dust, and remove the remaining bone in one piece. This not only affords greater protection against accidental injury of the membranous labyrinth immediately under the window, but so far there is every indication that the percentage of failure due to closure of the fenestrum has been greatly reduced.

The operative approach suggested by Poppen (66, 67) is said to be simpler

mately be made possible as a public health measure. One move in this direction was the establishment of pilot clinics in several of the counties of Maryland to determine the efficacy of nasopharyngeal radiation, supplemented when necessary by chemotherapy or surgical removal of tonsils and adenoids (4). Radium treatment of nodules of lymphoid tissue in and around the pharyngeal orifice of the Eustachian tubes has also proved to be a valuable addition to the standard measures used in the treatment of hearing impairment following recurrent attacks of otitis media (16, 21). During World War II the same type of radium treatment was used by the Army Air Force to prevent recurring attacks of aerotitis among its personnel (22 to 27) Asthma and asthmatic bronchitis due to bacterial sensitization, especially in children, has been treated successfully with radium alone or in conjunction with antibiotics, since it is so frequently due to chronic or repeated nasopharyngeal infections. However, here as in other maladies, radium treatment must not be used except after the most careful evaluation of the history and physical findings (28, 29).

A combination of amino acids with vitamins A, B complex, and C is said to improve several different types of hearing impairment (30), but on reading the paper it was our impression that these conclusions were not verified with adequate controls. Another publication reports improvement in both the perceptive and conductive type of hearing impairment, including otosclerosis, following injections of vitamin A (31). It is reasonable to expect improvement with this treatment if the hearing impairment is recognized in its earliest stages and is shown to be due to vitamin A deficiency, but it does not seem likely that cases of advanced impairment could respond favorably, considering the findings of Melanby (32), Loch (33), and Perlman (34). Marked improvement in hearing in early cases of central nervous system syphilis was obtained after treatment with penicillin by Loch & Tucker (35), but no improvement was noted in half of the patients with long standing deafness In this latter group, the damage to the cochlear nerve is irreparable.

Pohlman (36) reports that a marked improvement in hearing may be obtained in some patients by placing an acoustic probe against the round or oval window, or the fenestrum in the semicircular canal Ruedi & Furrer (37) discuss the experimental and clinical aspect of acoustic trauma in industry and war. They have devised an ear defender that withstood experimental test, but from the description we suspect it is too large and cumbersome to be practical for the soldier or the factory worker.

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strated by Dandy (41) in 700 patients, is a most satisfactory procedure. It stops the attacks of vertigo and does not destroy the hearing. In fact, the hearing of many patients improves following this operation (42). In contrast, the other surgical measures employed in Ménière's disease aim to destroy the membranous labyrinth, either through the horizontal canal or the vestibule (43, 44). This is far from the ideal therapy. It stops the attacks of vertigo but totally destroys the hearing and therefore is not suitable when the disease is bilateral. A completely different approach is recommended by Passe & Seymour (45). They remove the stellate ganglion, cut the fibres of the thoracic rami communicantes I and II and strip the vertebral artery. In patients so treated, both the vertigo and the tinnitus disappear, and in addition, the hearing improves. If these results prove to be consistent and permanent in a large number of cases, this operation should certainly receive precedence over all other surgical methods.

### Broncho-Esophagoscopy

The Jesberg (72) 3 and 4 mm. tubes make it easier and safer to bronchoscope infants. The greater lumen and smaller outside measurement of these tubes are possible by the use of a new miniature light bulb. Heathy & Emerson (73) report a series of 50 bronchoscopic examinations of infants for respiratory difficulty within the first 48 hr. after birth. There was no postoperative shock, and tracheotomy was not necessary in any of them.

Broyles (74, 75) has perfected a bronchoscope with a series of lens systems which can be passed through the tube when a clear and magnified view of the bronchi in the upper, middle, and lower lobes is desired. The lens systems are similar in construction to those in a nasopharyngoscope or cystosope. One of these, the retrograde telescope, has made it possible for the first time to view the upper lobe bronchi for infection, foreign body, or new growth. Broyles also uses a stream of compressed air across the end of the bronchoscope to protect the face and eyes of the operator from mucus and secretions that may be coughed out, and to prevent fogging of his glasses.

The permanent alnico magnet has proved to be a valuable aid in the removal of foreign bodies from the air and food passages. Equen (76) was not the first to use the magnet for this purpose, but he has extended and popularized its use. Under roentgen ray guidance, foreign bodies have been removed from the duodenum, stomach, esophagus, and bronchi. The magnet is small enough to be attached to a silk thread and swallowed, attached to a flexible catheter, or brazed to a brass rod for use through a bronchoscope.

Clerf (77) insists that hoarseness lasting longer than a few days, unless part of an acute upper respiratory infection, always calls for an examination of the larynx and such other studies as may be indicated The reason for this is that hoarseness is the first symptom of cancer of the larynx It should be widely publicized that delay in diagnosis may be extremely serious. Many patients do not seek medical advice until the growth is incurable. Syphilis can be a possible explanation of hoarseness, but it is not a common laryngeal

than all other methods. He thinks the window should be placed in the cupola of the vestibule. The skin incision is anterior to the external auditory canal, and when the cartilaginous wall is reached all further dissection is subperichondrial in order to avoid injuring the facial nerve or the parotid gland. The tragus and cartilaginous part of the meatus is retracted posteriorly, and the entire anterior bony wall removed down to the annulus membranae tympani. One advantage of this approach is the removal of a minimum of bone in the mastoid region, another is that it affords an excellent exposure of the attic, the peritubal, and hypotympanic cells and the tensor tympani muscle, all of which should be removed in certain types of chronic suppurative otitis media. An objection to the Poppen fenestration technique is the difficulty in adequately removing the periosteal bone at the site of the window. Meltzer (68) finds that when the hearing is not improved by the first fenestration it can never be restored by a second operation. Even when the hearing has been restored temporarily, revisions are successful in only about 30 per cent of the cases.

Biochemical studies (69, 70) have given no clue to the etiology of otosclerosis. The histologic study by Guild (71) shows that otosclerotic areas do not always involve the foot plate of the stapes, but are often found in areas far removed from the oval window. When the otosclerotic area does not involve the foot plate of the stapes, it is impossible to make a clincial diagnosis of otosclerosis. In Guild's series, in only 6 of 81 ears with histologic otosclerosis would it have been possible to make a clinical diagnosis of this disease. In 45 ears, the otosclerotic area was less than 0.1 mm. from the stapedial foot plate, but serial sections showed no ankylosis. In 33 ears with histologic otosclerosis, the hearing was impaired for high tones and good for low tones Guild's conclusions are based on the study of beautifully preserved and stained serial sections of 81 temporal bones and correlated with the audiogram of each patient made in a sound proof room shortly before death. Otosclerosis being an hereditary malady, it would seem important to advise patients suffering from this disease to have no children However, from the foregoing figures, it is evident that only a very small proportion of such patients can be recognized clinically, and therefore this is a discouragingly ineffectual way of dealing with the problem. By the same reasoning, a negative family history is of no value in determining whether or not a conductive type of deafness is due to otosclerosis.

*Ménière's disease*.—The etiology of Ménière's disease is still unsolved. Selfridge (38) thinks it is due to chemical changes. Atkinson (39) obtained favorable results with vitamins. Dramamine, which was found by Gay & Carliner (40) to be almost 100 per cent effective in the prevention and cure of motion sickness, is still being investigated to determine its therapeutic effect in Ménière's disease and other types of dizziness. A drug may be found eventually that will prevent the violent attacks of vertigo, but at the present time surgery is the therapy of choice for the severe and disabling form of Ménière's disease. Intracranial division of the vestibular nerve, as demon-

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disease. Too often a positive seriologic test is considered sufficient to establish the diagnosis, only to find later when the laryngeal condition fails to improve under antisyphilitic therapy that the real cause is carcinoma or tuberculosis. Carcinoma often begins on the anterior half of a vocal cord, tuberculosis usually begins in the posterior part of the larynx, while syphilis manifests a preference for parts of the larynx other than the vocal cords.

Lorhan & Roberts (79) discuss anesthesia in endoscopic work and report 96 cases in which they used curare-thiopental sodium. With the patient on the bronchoscopic table, the curare preparation is slowly injected into an arm vein. When the jaw muscles relax and it becomes difficult for the patient to raise his head from the pillow, thiopental sodium (Pentothal) is injected until the lid reflex is abolished. After this only a small amount of pentothal is necessary to maintain a state of anesthesia sufficient for the usual endoscopic examination. Muscle tonus is quickly restored at the conclusion of the examination by the intravenous injection of 2 mg. of picrotoxin. For children, a barbiturate or a small dose of morphine is given, but is safer to use no local or general anesthesia for the bronchoscopic examination. In adults however, relaxation of the musculature of the larynx, pharynx, and neck is essential for a satisfactory examination. Other investigators have also found that curare adds to the safety of thiopental sodium anesthesia by preventing laryngeal spasm and obtaining muscular relaxation with the minimum of pentothal (80, 81).

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# HEMATOLOGY

## Blood Formation and the Anemias

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The immense postwar literature on hematologic subjects is heavily infiltrated by biochemical and biophysical techniques. However, the everyday practice of medicine lacks the tools, time, and techniques to apply much of the increased understanding of normal and pathological physiology thereby gained, and the science heavily outruns the art. Because of the great volume of literature, space permits consideration only of the anemias in this review.

It is not always easy to distinguish between interference with erythrogenesis and with hemoglobin synthesis in the anemic state. Current investigative endeavors increase our comprehension of these mechanisms by studying (*a*) deprivation of the organism of individual metabolites; (*b*) the distribution in the body of essential metabolites radioactively tagged; (*c*) continued application of biochemical techniques to discover essential transport mechanisms.

Our innocence concerning many of the essential processes in the manufacture of cells is marked by the recent discovery of Plum (1) that in culture red cells may be produced from the nucleate normoblast by "gemmation," or budding, and the rediscovery of "motile" erythrocytes indicates this as a possible mechanism in the marrow.

Anemia may result from (*a*) failure to secure adequate hemoglobin manufacture, (*b*) failure to deliver adequate numbers of red cells (dyshemopoiesis); or (*c*) hypernormal blood destruction (hemolysis).

### BLOOD FORMATION

#### Synthesis of Heme

Previous studies, particularly those of Whipple, had indicated mammalian synthesis of the pyrrol precursors of deuteroporphyrin Shemin *et al.* (2) traced $N^{15}$ tagged glycine as a precursor of cell porphyrin in both man and rat and also showed that labelled acetic acid (deuteroacetate) is incorporated (3), the alpha carbon, not the carboxyl being used [Grinstein *et al.* (4),] Nucleate red cells of the duck and, strangely, also human sicklemic red cells. can synthesize porphyrins *in vitro* (5).

#### Erythrocyte Protoporphyrin

Discovered in the red cells by van den Bergh & Hyman in 1928, its variations in disease have been widely studied by Watson and various colleagues (6, 7) The erythrocyte porphyrin of young red cells (reticulocytes) is greater than that of mature cells (6, 7, 8). The normal level is 30 μg. to 45 μg per 100 cc. of blood and it is raised in reticulocytes, in iron deficiency

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## Siderophilin

Iron is transported in the serum, bound to a specific $\beta_1$-globulin (20), with a molecular weight of about 90,000, each molecule of which can bind two molecules of iron. This protein comprises about 3 per cent of the total serum proteins and normally offers a total iron binding capacity of about 350 μg. of iron per 100 cc. of blood. It is normally about 35 per cent saturated, representing a serum iron level of about 100 μg. per 100 cc

This protein, named siderophilin, has been studied in health and various hematologic states by Laurell (21), by Cartwright & Wintrobe (22) and by Finch (23). The total iron binding capacity is depressed in infection, in cirrhosis, and in the cachectic state. The percentage saturation is naturally low in hypochromic anemia and also falls in infection. Conversely, it is high in pernicious anemia and hemolysis, while in hemochromatosis and transfusion hemosiderosis it is completely saturated. It is probable that not all the pathologic variations in this transport protein have been revealed

Prolonged suppurative infection lowers the serum iron and elevates the serum copper (10, 24).

## Iron Therapy

In the footsteps of Capell (1930), and quoting Heath and also Witts ("parenteral administration of iron is unpractical, dangerous and unnecessary"), Goetsch, Moore & Minnich (25) gave 0.608 to 1 32 gm iron as colloidal ferric hydroxide by single infusion to eight patients. Severe toxic responses occurred in six. From 71 per cent to 99 per cent of the injected iron was utilized, with a resultant superior reticulocyte response Similarly, effective utilization of intravenous radioactive iron was demonstrated by Finch *et al* (26)

Occasionally, rare cases are met in which effective and safe parenteral iron therapy might offer a potential advantage, e g patients who are utterly iron intolerant, those with ulcerative colitis, and those with steatorrhoea or who fail to absorb iron for unknown causes. Nissim (27a, 27b) has developed a 1 per cent solution of saccharated ferric hydroxide in sucrose (later 2 per cent), which may be given in doses increasing to 300 mg. of elemental iron. Local thrombosis and marked systemic or renal reactions are not encountered Davidson & Girdwood (28) have used such preparations successfully in iron-resistant hypochromic anemia, while Stock & Wilkinson (29) have treated ten cases with a commercial preparation. Govan & Scott (30) have treated 25 cases of hypochromic anemia of pregnancy, two of which were known to be iron-resistant. Considerable masses of iron may obviously be introduced in this way and there is imminent danger of causing therapeutic hemosiderosis, which was not a consideration so long as the "mucosal block" restrained the absorption of oral iron.

## Nonferrous Metals in Hematopoiesis

*Copper.*—This element is present in the red cell, but there is little infor-

(500 μg. to 600 μg.-per 100 cc.), and in various toxic anemias (7, 126), including lead poisoning. It is low in Cooley's anemia (7) (which may depend on the failure to synthesize porphyrins correctly) and in experimental pyridoxine deficiency (9), which produces a somewhat hypochromic anemia. In general, though not invariably, the serum iron level and the erythrocyte porphyrin levels are inversely related and the serum copper level usually rises when the serum iron level falls (10, 126).

## Iron Transportation

The rediscovery by Laufberger in 1937 of an iron containing protein "ferritin," and its further intensive study by Granick (11) together with Michaelis (12), adds a helpful concept to the mechanism of duodenojejunal iron absorption. Ferritin has a molecular weight of about 460,000 and contains from 17 per cent to 23 per cent iron (12). This iron is readily removable leaving the iron-free protein apoferritin. The iron is believed to exist in the ferritin as an adsorbed micelle of colloidal hydroxide (13). Ferritin is richly distributed in the spleen, liver, and red marrow of the horse and the human, but is much less in other animals. Granick (14) has shown that its presence in the duodenal mucosa of the guinea pig, normally small, is greatly enhanced by feeding iron, and it is thought that apoferritin is immediately synthesized to meet the need. Sensitive precipitin reactions fail to show ferritin in the circulation. However, when radioactive hemoglobin is transfused into anemic dogs, radio iron is recovered from splenic ferritin (12) and so must be concerned with released iron from hemoglobin breakdown.

The problem as to what factors control the absorption or rejection of gastrointestinal iron in the absorbable state (the "mucosal block") remains unsettled. Granick (14) has postulated the activity of ferritin in a redox system controlled by the tissue tension of oxygen. However, he failed to explain the previously observed fact (Hahn *et al.*, 1939) that in dogs the absorption of radio iron is related to the grade of hemorrhagic anemia Also, in humans who were fed test doses of iron the elevation of serum iron thereafter is not controlled by the anemia (Moore *et al*, 1939).

The natural assumption that variations of apoferritin production might cause defective iron absorption in clinical conditions remains unstudied. In hemochromatosis (15) ferritin is present in normal quantities, relative to the amount of iron present, and Granick (12) assumes that the iron is present in abnormal configurations, thus allowing high concentrations Hegsted, Finch & Kinney (16) found that rats fed a normal diet did not absorb excess iron, but on a defective diet (corn grits) iron accumulated in the liver, thus indicating one possible mechanism in the "mucosal block" Excess dietetic phosphate reduced iron absorption (17), an old fact confirmed, but the "hemoglobin regenerating liver fraction" of Whipple and Robscheit-Robbins does not influence the absorption of radio iron (18).

Injection of 700 mg. of iron as ferritin within six days cured hypochromic anemia with marked epithelial changes during pregnancy (19).

series of discoveries of related factors from many sources, essential to growth in the more primitive organisms and to hematopoiesis in fish and birds, all ultimately identified as related to, or identical with, the folic acid recovered from spinach leaves (Mitchell, Snell & Williams, 1942). This substance was synthesized in 1945 (41) as pteroylglutamic acid (42a, b, c, d).

Hematologic remission produced by folic acid in pernicious anemia was first reported by Spies *et al.* (43) in 1945. Confirmation of this activity and the response of other megaloblastic anemias was immediately published (44) and shortly extensively confirmed (42c, 45 to 48). In most cases of pernicious anaemia full hematologic remission is produced by oral doses of 5 μg daily. Less than 3 μg. per diem is apt to produce incomplete responses [Spies (43)]. The average dietary intake of folic acid has been stated to be approximately 1.4 μg daily (49). Unlike that of microorganisms, for which they are metabolic blocking agents, the human economy can utilize the multiple glutamic conjugates (di-, tri-, and hepta-glutamates of folic acid) (50a, b, c). However, variations in the pterin ring side chains render folic acid complexes inutile (51).

The early belief that folic acid is the essential antipernicious anemia factor of liver extract was quickly tempered by the realization that the compound is rejected in the first precipitation in the preparation of Cohn's Fraction G and therefore the folic acid content of active liver extract is small. Moreover, there were early reports of incomplete (52, 53) or unsustained (53, 54) hematologic responses. Additionally, the occurrence of neurologic relapse, on occasion severe, after satisfactory hematologic response (42, 45, 47, 48, 52, 54 to 59), was foreign to previous experience with refined liver extracts.

Quite evidently, folic acid is not the neurotropic factor, and it was postulated that folic acid might even block neurotropic enzyme systems or, at its simplest, glutamic acid itself (56). However, pteroylglutamic acid does not influence glutamic acid usage in the excised rat brain (60).

In all, 13 authors, discussing about 140 patients with pernicious anemia treated by folic acid, report about 40 instances of neurologic relapse, with the onset some time following two months' therapy and without relation to previous neuropathy. It may be properly considered at this time that pteroylglutamic acid alone is not a suitable long-term therapy for cases of pernicious anemia.

As a possible clue to the fundamental defect in pernicious anemia, Spies *et al.* (61) noted, in three patients, that 4.5 gm daily of the pyrimidine thymine fed orally produced reticulocytosis and a return of the blood count to normal. Folic acid may share in the conversion of thymine to the nucleoside thymidine. However, two out of four patients with subacute combined degeneration of the cord deteriorated rapidly on the same dosage (62).

Three grams daily of thymine maintained three patients with sprue for twelve months (63). However, adenine, another constituent of thymonucleic acid, in doses of 2.5 gm daily was hematologically ineffective and led to uremic manifestations in a case of pernicious anemia. (64)

mation bearing on its function and relative distribution therein. This is true of the position of copper in the human economy as a whole, the duties of the proteins, hemocuprein from serum and hepatocuprein of liver, bearing 1 34 per cent copper (Mann & Keilin), being unknown at this time. The fact that copper is essential to heamtopoiesis in the rat (Hart *et al.*) has led to the insecure assumption that this must be true in the human. Hypercupremia characterizes many anemic states, copper values tending to rise when iron values fall. But low copper values (below 3$\mu$g. per cent) are extremely rare and are not usual in anemic states.

*Cobalt.*—The discovery of cobalt in vitamin $B_{12}$ revitalized the previous interest in the position of this metal in hematopoiesis, originally conditioned by cobalt polycythemia. Absence of cobalt from the soil caused "coast disease," a hypochromic anemia of ruminants, curable by setting out cobalt licks, but not by injection of cobalt salts (31), nor by the injection of vitamin $B_{12}$ (31). Goll *et al.* (32) showed that alteration in the proruminal bacterial flora, dependent on cobalt, induced the anemia. Further inquiry as to exactly how this anemia depends on the flora might be instructive. Wintrobe *et al.* (33) showed that cobalt feeding prevents pseudo-infectious (turpentine) anemia in rats, but, curiously, not the concomitant hypoferremia. In applying this observation to clinical instances of inflammatory anemia, Robinson *et al* (34) and also Berk *et al.* (35) discovered that cobalt will elevate depressed counts when given orally. Some years ago, Barron (historic personal communication, 1939 to 1940) suggested that cobalt polycythemia was compensatory to a postulated toxic interference with oxygen transfer enzymes. Hence, until more is known of its mechanism cobalt therapy of infectious anemia is not advocated, with which statement the cited authors concur.

*Molybdenum.*—This element, essential to the manufactue of chlorophyll, of which it is not a component part (36), is claimed to potentiate iron in the therapy of hypochromic anemia of pregnancy (37) and to have caused responses in iron-resistant hypochromic anemia (38). Convincing data are yet lacking.

## Vitamins in Hematopoiesis

The vitamins, being enzymes or coenzymes essential to anabolic processes, are not as yet fully assessed as to the various degrees to which they contribute to the anabolic process of hematopoiesis Reference to the review of Cartwright (39) and to the Gould Research Foundation Symposium on Nutritional Anemia (40) will reveal recent views in a complex literature. To quote Cartwright (39):

> It has now been definitely shown that riboflavin, pyridoxine, nicotinic acid and the various folic acids are important for red cell production in at least one species each. The role of ascorbic acid, pantothenic acid, choline, and biotin are indeterminate, and there is no substantial evidence that thiamine, para-aminobenzoic acid, or inositol is concerned

*Folic acid*—The development of experimental megaloblastic anemia in monkeys (Day, 1937) and its prevention by vitamin M was the prelude to a

pernicious anemia with vitamin $B_{12}$ (71, 73, 75 to 80). It may be safely stated that any megaloblastic anemia not responding to 1 μg. of injected vitamin $B_{12}$ daily is not uncomplicated pernicious anemia. Vitamin $B_{12}$ derived from *S. griseus*, is as effective as that derived from liver extract (81).

*Vitamin $B_{12}$ is highly effective in the treatment of Addisonian neuropathy* (73, 76, 78, 79, 81, 82, 83). Previous experience with liver extract would lead us to expect such results. There is no possible reason to suppose that pure vitamin $B_{12}$ can be more effective than the equivalent dose of refined liver extract, nor to suppose that it will benefit those neuropathies which have not already displayed a response to such therapies. Vitamin $B_{12}$ is a new therapy only in its purity and in its quantitative availability from new sources

## ANEMIC SYNDROMES

### Megaloblastic Anemias

*Pernicious anemia.*—An authoritative review of this subject has been submitted by Wilkinson (84). Elucidation of the folic acid-vitamin $B_{12}$ complexes has increased greatly our critical knowledge of the nature of megaloblastic anemias as a group, but the essential lesion in pernicious anemia remains elusive. It is not much doubted that this defect is primarily in the stomach. In confirming previous experiments of Wilkinson on the origin of "hemopoietin," the gastric factor, Landboe-Christensen & Plum (85) found that powdered human fundic stomach produced an active, and powdered human pyloric stomach produced a moderate, reticulocytosis in two patients in relapsed pernicious anemia, bearing out the theory of the fundic origin of the intrinsic factor. In the hog, previous experiments of Meulengracht had indicated the pyloric stomach and duodenum to be rich in the intrinsic factor, in confirmation, pure duodenal juice of hogs was curative in the presence of a good diet (86). Bethell *et al.* (74) showed that fractions from hog duodenum could produce reticulocytosis when fed with vitamin $B_{12}$ Probably of great significance, and a potential key to the mystery, is Fox's discovery (87) of a nonpeptic, nontryptic, proteolytic enzymatic activity *at pH 7.4, present in normal gastric juice, absent from the gastric juice* of pernicious anemia (87, 88), and present in diminished quantities in sprue (88).

Bony decalcification on a familial basis has been related to achylia gastrica of the pernicious anemia type (89) The required time for anemic relapse after discontinued therapy was over 26 months in six out of twelve patients; the remainder relapsed in 8 to 18 months, and an increased output of stool urobilinogen was the earliest indication of relapse (90). Rundles (91) identified olfactory and cerebral types of neuropathy in addition to the posterio-lateral sclerosis and peripheral neuropathy, and noted that the prognosis in

at this time be interrelated. Thus, vitamin $B_{12}$ is promptly effective (76,

*Vitamin* $B_{12}$.—It being clearly evident that pteroylglutamic acid was not the cause of the antipernicious anemia activity of highly refined liver extract, *in 1948* the responsible agent was identified from liver as a red pigmented substance by Smith (65) of the Glaxo Laboratories in England and simultaneously by a large group of workers (66) in the Merck Laboratories in New Jersey. The latter first crystallized Vitamin $B_{12}$ and identified it with a red pigment obtained from *Streptomyces griseus* as a by-product of streptomycin production (67).

Vitamin $B_{12}$ has a molecular weight of about 1,200 and contains one atom of cobalt (4 per cent) in each molecule. It is evidently widely distributed in nature and would appear to be yet another of those enzymes or coenzymes fundamental to protoplasmic anabolism. In that either thymidine or desoxyribosenucleic acid can substitute for vitamin $B_{12}$ in the life of certain microorganisms, it is probable that this enzyme is responsible for the construction of nucleoprotein and possibly converts thymine to thymidine (68). The activity *of pteroylglutamic acid and vitamin* $B_{12}$ *do not overlap in the growth* of microorganisms, or chicks, or in the cure of leucopenia-anemia in folic acid-deficient rats (69). Also, the anemia of folic acid defective pigs is not cured by refined liver extract (70, 70a) and it is clear that for the pig both folic acid and vitamin $B_{12}$ are essential. In view of the uncontrollable production of vitamin $B_{12}$ in the gastrointestinal tract of the human patient, it is difficult to prove that the same conditions obtain in human hematopoiesis. Nevertheless, rather uncritical clinical experiences point to the necessity for both factors in the human.

Randolph West (71) reported that the first three patients with pernicious anemia to be treated with vitamin $B_{12}$ in the United States showed some response to as little as 5 $\mu$g of crystalline $B_{12}$ injected. It is now generally agreed that 25 $\mu$g. injected will produce almost complete remission in most instances of true pernicious anemia, and that 1$\mu$g. injected daily is about the equivalent of one unit of injected liver extract The duration of the response would seem to be about that of the equivalent liver extract.

When fed by mouth, vitamin $B_{12}$ will not cure pernicious anemia (72, 73, 74), unless at the same time normal human gastric juice is administered [Berk *et al.* (72)]. Bethell *et al.* (74) have concentrated dried hog duodenum, so that 1 gm. of concentrate fed together with 5 $\mu$g. of vitamin $B_{12}$ produces hematologic response.

It is concluded that vitamin $B_{12}$ may be the extrinsic factor of Castle and Strauss [Berk *et al.* (72)] At this time the conclusion that folic acid (or some related pterin) is the intrinsic factor is not justified. In this connection the long overlooked work of Jacobson (1939) on the absence of the argentaffine system of cells from the gastrointestinal tract in pernicious anemia (he identified the argentaffine quality as due to pterins in the cell) is of proper interest.

The cobalt content of vitamin $B_{12}$ led West & Riesner (75) to show that pernicious anemia does not respond to 150 mg , nor to 500 mg. of cobaltous salts fed daily by mouth.

Considerable experiences has accrued in the treatment of [illegible]

only two that were resistant to highly refined liver extract. However, it is reasonably certain that in temperate climes megaloblastic anemia occurs due to failure to ingest or absorb nutritional factors, which is resistant also to refined liver (42c, 107, 109, 111) or to vitamin $B_{12}$ (73), and which Wilkinson would have called "achrestic anemia." Such cases responded rather uniformly to folic acid, to transfusions with improved diet (110) or to proteolyzed liver (109).

*Tropical sprue*.—This disease was effectively treated with folic acid (112, 113, 114) and by folic acid conjugates (106, 115), by vitamin $B_{12}$ (77, 79), and by 3 gm. daily of thymine over one year (63). Suarez *et al.* (113) stated that folic acid reduced the diarrhea, but the fat content of the stool remained high. Authors dealing with tropical sprue did not draw particular attention to partial failure, whereas authors reporting nontropical sprue (idiopathic steatorrhea) noted some instances of incomplete remissions and failure to maintain the blood count in the absence of therapeutic liver extract (42c, 47, 113, 116) Occasionally, larger doses of folic acid than usual were required (113). In celiac disease results of folic acid therapy were disappointing (42c, 117).

*"Pernicious anemia" of pregnancy*.—Folic acid is effective in the pernicious anemia of pregnancy (42a, 44, 109, 118, 119), which may respond to, or resist, refined liver (118).

*Megaloblastic anemia of infancy*.—This disorder escaped recognition until properly defined by Zuelzer & Ogden (120) in 1946 Occurring for the most part in infants aged 3 to 6 months with feeding problems, the peripheral blood is commonly normocytic and normochromic and there may be thrombocytopenic hemorrhagic phenomena Such a peripheral pattern does not immediately suggest a megaloblastic marrow. The anemia responds to refined liver (120), folic acid (120, 121, 122) and to vitamin $B_{12}$ (73a), although with this latter agent some failures have been reported (123). In this connection, it is noted that pteroylglutamic acid sharply limits the large hydroxyphenol excretion in the urine of some premature infants fed tyrosine, as does folic acid-free liver extract (124). The hypernormal excretion of hydroxyphenols observed in pernicious anemia is also sharply limited by liver extract (125).

## Refractory, Agnopathic and Toxic Anemias

At this time so little is really known about the growth and differentiation of bone marrow that anemias of this general order are accounted for on a merely recitative morphologic basis and cannot be related one to the other on the basis of pathologic physiology. Deficiencies or intoxications, which produce one mode of morphologic change in a given species, may produce an entirely different mode in another, e g. folic acid deficiency in the rat produces aplasia of the marrow but a megaloblastic hyperplasia in man. The site, chemically speaking, of intoxicative actions is not known.

*Anemia of infection*.—This, in part, has been discussed above. During inflammation the serum iron falls, the serum copper rises (24, 126) and,

92, 93). By way of contrast, the response to folic acid is absent or irregular (92, 93, 94). Thymine is inactive (92). Brown (94) has regularly produced a cure of the glossitis with pantothenic acid, and irregularly with nicotinic acid. This and the recent incrimination of pantothenic acid deficiency as a cause of the "burning feet syndrome" offers the first evidence of any activity in humans.

*Anemia of total gastrectomy.*—MacDonald *et al.* (95) collated a total of 41 cases of total gastrectomy from the literature; 29 did not develop anemia, 10 of which had definitely not received any prophylactic liver, and 12 cases developed macrocytic anemia. Such anemia is readily responsive to liver extracts and also to folic acid (96) (the problem of general body nutrition is not readily responsive).

*Gastrointestinal anastomoses.*—Short-circuiting operations on the gastrointestinal tract may result in macrocytic anemia (97) or glossitis and steatorrhea (98). Brown (98) claims that the anemia may be cured by highly refined liver extract, marmite, or calcium pantothenate with inositol, but not by niacin, thiamin, or riboflavin. Experimentally, the analogous anemia may be produced regularly only if the blind entero-enterostomy pouch is arranged to be content filled rather than drained (99a, 99b).

*Dibothriophyllum latum anemia.*—The studies of Bonsdorf (100a, 100b) appear to have crystallized the terms, hitherto vague, under which infestation will or will not produce anemia. Only a high position in the duodenum produces anemia; hence, only a proportion of the infested are anemic, a shifting worm may change the anemia, and reinfestation does not imply recurrence of anemia. Some patients do not recover after vermifuge without liver extract (101). Twelve out of 24 patients, recovered from tapeworm anemia, had alcohol or histamine achylia (102), which may significantly relate the occurrence of anemia to gastric factors.

*Nutritional megaloblastic anemia.*—This syndrome can arise from deficient supply of vitamin $B_{12}$, folic acid, and possibly also other factors, e g. choline (103) and pantothenic acid (98). Failure to absorb these factors or their interaction products may assist in conditioning the cause, and hence the purely nutritional nature of any given case is often not crystal clear. Also, the exact relationship between the nutritional factors allegedly deficient is far from clear And thus vitamin $B_{12}$ and pteroylglutamic acid are often, but not always, interchangeable, and evidently either of them may be supplanted by large doses of thymine.

Nutritional megaloblastic anemia (of which tropical macrocytic anemia is regarded as only a geographic variant) has been repeatedly cured with folic acid (42c, 77, 103, 104, 105) and its conjugates (106), and it has responded to vitamin $B_{12}$ (73, 77, 79, 106) Wills (1934) had claimed that a considerable proportion of cases of tropical macrocytic anemia would not respond to highly refined liver extract (Anahemin), that is, presumably to $B_{12}$-rich liver extracts, but would respond to crude extracts. Her conclusions have been exposed to some question, e g. Patel & Bhende (108) who, studying 45 patients with megaloblastic marrows and with free gastric acid, found

11 per cent) is accompanied by marrows showing progressive hypoplasia and increasing content of plasmacytes and reticulum cells. There may be deafness, skin pigmentation, and congenital deformities. Nothing is known of the nature of the metabolic fault. Fanconi (153) described another syndrome, involving anemia, with rachitic dwarfing, hypophosphatemia, acidosis, glycosuria, and cystine amino-aciduria, in which sternal marrow puncture may deliver recognized cystine crystals.

*Congenital aregenerative anemia*—Complete absence of erythropoietic cells in the marrow was seen at 17 months of age in a Group A infant whose mother possessed anti-A titer, alleged to reach 1:128,000 (154).

Other extraordinary anemic syndromes of unknown nature are recorded. Two members in the same family died with proliferative arteritis and anemia characterized by a high proportion of iron-containing circulating red cells, "siderocytes" (155). In children severe anemia and fever accompany an extensive deposition of iron in the lungs, producing characteristic x-ray appearances in the fatal syndrome named "acute pulmonary hemosiderosis" (156, 157). This disease has been diagnosed antemortem. Another agnopathic anemia in a 37-year-old male was characterized by highly deformed red cells and a hyperplastic erythroid narrow with 55 per cent of multipolar and otherwise deformed mitotic figures in dividing normoblasts (158).

The claim of benefit in three cases of aplastic anemia (probably due to

[illegible]

*Sicklemia and sickle cell disease*—Pauling *et al.* (163) believe the essential lesion in this disease to be an inherited anomaly in the structure of hemoglobin The patient with sickle cell disease is believed to be homozygous, and he with the trait supposedly heterozygous (164), thus possessing only 50 per cent of hemoglobin which changes molecular configuration in the presence of carbon dioxide. Rapid tests for sickling depend upon removing the oxygen or raising the carbon dioxide by exposing red cells to reducing agents (165, 166, 167) or to microorganisms (168)

The heart in sickle cell disease is generally assumed to be that of chronic anemia. Rheumatic heart disease was found in 5.6 per cent of sicklemics at Cook County Hospital (169), not markedly in excess of the expected incidence Prolongation of the P-R interval occurs quite frequently in sickle cell disease and may be due to sicklemic vascular occlusions (170). Curiously, infant blood does not sickle well due, perhaps, to its content of fetal hemoglobin (171), although fatal sicklemia has occurred at one month (172). *In vitro*, the development of sickle cells is prevented by inhibitors of carbonic anhydrase (173), most of which are vigorous poisons Normal red cells survive well when transfused into the sicklemic (174), but sicklemic cells are stated not to survive well in the normal (175), although other workers hold that this is not true (176).

*Mediterranean anemia.*—The incidence of thalassemia minor in the Italian population of Rochester, N. Y. is 4 per cent (177). It is not entirely

cellular porphyrins rise (126). There is some depression of the total iron binding capacity of the serum (22). The influence of cobalt on these changes is discussed above. During fever there is more iron absorbed than is converted into hemoglobin, even in patients with adequate iron stores (127).

*Anemia of trauma.*—This has not been adequately studied. Little is known of copper, iron, and porphyrin changes, but the constant negative nitrogen balance is striking, and possibly associated with the failure in protein synthesis (128).

*Anemia of hepatic cirrhosis.*—In this anemia the circulating red cell mass may be normal and the anemia be due to hypervolemia (129). Jarrold & Vilter (130) studied 30 proven cirrhotics and found 65 per cent with moderate to severe macrocytosis The reticulocyte level was up to 8 per cent and the constant marrow plasmacytosis, up to 4 per cent, rose with rising globulin levels. In only 3 out of 30 marrows examined by them were there megaloblasts, while in another series of 25 cases there were none (131).

*Anemia due to chemicals*—Early in intoxication there is hyperplasia, later followed by hypoplastic, acellular medullary tissue New chemicals appear on the list of potential causes Tridione caused leucopenia (below 1,600 cells per cubic millimeter) in 6 3 per cent of patients (132), and caused "acute aplastic anemia" (133), "fatal acute pancytopenia" (134), and "abnormal marrow" (135) The related compound Mesantoin has been associated with similar variations of aplasia (136, 137, 138). The human marrow concentrates atabrine (139, 140), which has been associated with aplasia more often than has been published. Streptomycin (141) and Thorotrast (142) have been incriminated. Erythrol tetranitrate apparently caused a unique, fatal anemia, characterized by the presence of Heinz bodies in 13 per cent of the red cells (143). In lead poisoning the stipples were shown to be partly iron (144), but the non-iron part of the stipple is probably ribose nucleic acid and points to defective formation of "heme" (145).

*Idiopathic aplasia of the marrow*—This mysterious occurrence has been reported in association with Simmond's Disease (146).

*Diffuse fibrous dysplasia of the marrow (myelosclerosis)*—This disease is commonly associated with acute forms of tuberculosis. On the basis of four instances, Koch's bacillus is believed by Crail *et al.* (147) to cause the syndrome. An allergic theory (148) is also propounded At this time it is of interest to note the occurrence of a diffuse fine fibrosis produced by chronic exposure to folic acid blocking agents in leukemic marrows, and also that an infectious osteopetrous lymphoma has been known in fowls for some years

*Subacute idiopathic hypoplasia of the marrow.*—"Progressive myeloid atrophy" was described by Ferrata in 1939 and exists as a clinical entity (149), but is distinguished from more acute forms of hypoplasia only by its slower progress.

*Familial hypoplasia of the bone marrow (Fanconi syndrome).*—This rare, inborn error of metabolism becomes evident in juvenile or younger adult years and was recently described in three families (150, 151, 152). Peripheral pancytopenia with hemorrhagic tendencies and some reticulocytosis (3 to

11 per cent) is accompanied by marrows showing progressive hypoplasia and increasing content of plasmacytes and reticulum cells. There may be deafness, skin pigmentation, and congenital deformities. Nothing is known of the nature of the metabolic fault. Fanconi (153) described another syndrome, involving anemia, with rachitic dwarfing, hypophosphatemia, acidosis, glycosuria, and cystine amino-aciduria, in which sternal marrow puncture may deliver recognized cystine crystals.

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The claim of benefit in three cases of aplastic anemia (probably due to drugs) by large doses (200 to 400 mg. daily) of folic acid (159) has not found support in the experience of others treating chemically induced and agnopathic aplasias with folic acid in more usual doses (42c, 160, 161, 162)

*Sicklemia and sickle cell disease.*—Pauling *et al.* (163) believe the essential lesion in this disease to be an inherited anomaly in the structure of hemoglobin. The patient with sickle cell disease is believed to be homozygous, and he with the trait supposedly heterozygous (164), thus possessing only 50 per cent of hemoglobin which changes molecular configuration in the presence of carbon dioxide Rapid tests for sickling depend upon removing the oxygen or raising the carbon dioxide by exposing red cells to reducing agents (165, 166, 167) or to microorganisms (168)

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*Mediterranean anemia.*—The incidence of thalassemia minor in the Italian population of Rochester, N Y is 4 per cent (177). *It is not entirely*

clear, though it seems likely, that the inheritance of the Cooley trait or the Cooley syndrome depends on the monozygous or bizygous inheritance of a single defective genetic property (178, 179). The syndrome has been noted in Chinese (181) and Negro (180) persons. It has been associated with leg ulcers (182), biopsy showing much iron in the dermis. The essential lesion may depend on defective porphyrin synthesis, since erythrocyte values are low therein (7).

## Hemolytic Anemias

*Coombs test*—The antihumanglobulin rabbit serum of Coombs (183) has provided a most useful tool for the demonstration of red cells which have been "sensitized" by the attachment of antibodies. This may be used directly to test for antibodies attached to cells ("direct developing test"), or, by exposing a panel of cells of appropriate antigenicity to sera under test, it may be used to expose antibodies in the sera ("indirect test"). Its greatest usefulness in pragmatic medicine is to diagnose antibody development in the mother and the sensitization of the baby's cell in transplacental isoimmunization. Limitations to its usefulness are that the antibody may be attached to the cell only under certain critical conditions as to pH (184), and hence *in vitro* tests for attached antibody, including that of Coombs, may be negative. For some unexplained reason the Coombs serum will not detect cells senstitized by the Landsteiner agglutinogens (183). However, the range of antibodies to the Rh antigens (C-c, D-d, E-e, etc.), to the M-S-N-O system, to P, Lutheran, Jobbins and Kell-Cellano systems and others, are uniformly detected.

The rare, familial hemolytic ovalocytosis is redescribed (185, 186, 187). The late Cooley (251) reported one such cases, splenectomized beneficially shortly before his death. The rare hemolytic methemoglobinemia is described in two instances (188)

*Chemical and mechanical hemolysis.*—Quinine is a rare cause (189) of hemolysis in the absence of malaria, evidently acting as a direct hemolysin. Following varied sulfonamides, indirect hemolytic reactions with demonstration of agglutinin (190, 191, 192) or without demonstrable antibodies (193) are described. The injection of distilled water into the bladder during prostatectomy, a widespread urologic practice, is regularly followed by a large hemolysis and even the lower nephron syndrome (194) The need for a nonhemolytic, nonconducting irrigating solution is not yet filled.

*Hemolysinic and autoagglutinative acquired hemolytic anemia.*—In atypical pneumonia, in which syndrome cold agglutinins are present in 53 per cent of cases (195, 196), Finland *et al.* noted 11 cases of hemolytic anemia out of a total of 200 sufferers Such patients may develop anemia only after a cold sponge or other chill (197, 198). Cold agglutinins of apparently spontaneous origin may also be associated with hemolytic anemia (198 to 202), or with virus infection presumptive or identified, e g infectious mononucleosis (203). The Donath-Landsteiner test may be positive (203) or negative (200) in nonsyphilitic cases.

Cold agglutinins may be the apparent cause of Raynaud's syndromes (200, 201, 202, 204).

The cells of a syphilitic negro male were hemolyzed by the patient's serum in the presence of complement and carbon dioxide, prevented by 0 008 *M* sulphanilamide or 0.05 *M* cyanide (205a, 205b).

Hearst (1942) showed chicken erythrocytes were agglutinable by influenza and other viruses, which, as shown by the electron microscope (206), attach themselves to the red cell surface. After treatment with certain viruses e g. Newcastle disease virus, swine influenza, and influenza A and B viruses, human red cells become agglutinable by "incomplete" or blocking, antibodies (207, 208). Epidemic acute acquired hemolytic anemia, as described by the French School and improperly designated by the Lederer eponym, is usually a febrile disease, and electron microscopy of cellular surfaces might be very revealing.

Incubation of homologous cells with splenic pulp from four patients with aquired hemolytic anemias sensitized the cells to Coombs' serum. In contrast, three spleens from thrombocytopenic purpura, or congenital hemolytic anemia, did not do so Blood from three of the sensitizing spleens displayed marked spontaneous agglutination (209). This suggests, but does not establish, the fact of an immunologic reaction.

*Congenital hemolytic anemia* —In 1937 Heilmeyer drew attention to the role of nonhemolytic hypersplenism in the anemia of congenital microspherocytosis Owren (210) studied serially the pre-, intra- and postcrisis patterns in a third generation sufferer. At the sixth day there was virtual absence of marrow erythropoiesis, with marked resurgence at the tenth day. In six cases of congenital microspherocytosis in crisis he noted the absence of serum jaundice in the initial phase of anemia. He argued that acute hypersplenic inhibition of the marrow is shortly followed by anemia due to the very brief life of the abnormal microcyte Others (211) were quick to confirm the essential absence of signs of excess hemolysis as the cause of the anemic phase.

*Treatment of hemolytic anemia.*—Whereas the anemia of congenital microspherocytosis responds uniformly to splenectomy (Thompson, 1936), in acquired hemolytic syndromes different authors display the widest possible variation in enthusiasm for splenectomy (212) Two recent series offer limited comparative figures Fisher (212) splenectomized six out of fourteen cases, with two recoveries and one improvement, the unoperated eight cases enjoyed about the same prognosis Stickney & Heck's (213) series of 22 splenectomized patients contained eleven acquired microspherocytics, of which six did excellently; the eleven which were nonmicrospherocytic contained four that did not do so well but improved, while seven were unimproved. Unlike Fisher, these authors feel that operation offers the only hope. Evidently the microspherocytic pattern is most favorable.

*Transplacental and transfusion iso-immunization, erythroblastosis fetalis* — The entire pattern of our understanding of the problems involved in trans-

placental iso-immunization is confused by the incomplete catalogue of the antigens competent to develop antibodies in those not possessing them, and also by the incomplete analysis of the antibodies to which they may give rise. No simple statement can chart the path of understanding through these stormy seas and the brevity of this paper does not permit an attempt thereat. Suffice it to say that between the years 1941 and 1946 transplacental and transfusion iso-immunization developed four types of human antisera in mothers or transfused persons, which agglutinated constant, though individual, percentages of panels of Caucasian cells in such a manner that eight different types of blood cell were postulated. It became obvious that these antisera were identifying different antigens, and that a given red cell might contain more than one antigen. The followers of the historic school of nomenclature (the Rh school) were sorely tried by this development, postulated that red cell antigen inheritance might be polyallelic, and as each new type of red cell, distinguished by different proportional agglutinability was discerned, a new Rh suffix was devised to name it. Fisher [see Race (252)] extended the Bernstein A-O, B-O theory, suggesting that the variations observed would be explained by the inheritance of antigens associated in triads selected alternatively from six alleles C-c, D-d, E-e. As in the Bernstein theory, crossing is assumed, which permits eight possible combinations. Some of these variations are extremely rare, but all have been identified, and antibodies have been discerned against all the six allelic antigens Unfortunately, it seems that even this complicated arrangement of antigens is simpler than nature's own devices in the matter, and Race *et al.* have recently discerned transfusion iso-immunization sera that indicate that the C-c (214), and also the D-d (215) loci are not simple alternatives, but contain a spectrum of antigens within the group The phylogenetic history of man is probably written into these different inheritable proteins, and therefore continued discovery in the direction of complexity is anticipated. Some of these new subvariants have been identified in erythroblastic reactions (216). Outside the Rh family of antigens, new antigens are determined in iso-immunization reactions [M-S (217), N-S (218), Kell-Cellano (219, 220); Lewis (221); Jobbins (222)]. Following Boorman & Dodds (224) the A and B agglutinogens have been repeatedly incriminated in transplacental reactions [for references see Smith (154), though the serologic integrity of some reports may be questioned] Wiener *et al* (223) emphasize that the A-B sensitization may occur in the first pregnancy. The onset of hemolysis in the infant may be delayed for ten to twenty days (224).

Three orders of antibody have been clearly identified (225, 226) and Witebsky may have identified a fourth variant (227). First order antibodies are "complete" "bivalent" "saline agglutinating" antibodies and are usually assumed although questionably, to give positive Coombs tests; second order antibodies are "incomplete," "univalent" antibodies, which may inhibit the activity of agglutinating antibodies, and hence are "blockers," but in viscid solutions (albumen, gelatin) "conglutination" may occur. These are clinically the antibodies of highest importance. The third order are the "cryptaggluti-

noids," which do not block, conglutinate weakly, but give positive Coombs tests (225, 228). Agglutinating antibodies are γ-globulins; blocking antibodies are found in the albumen and α-globulin fractions; and cryptagglutinoids in *the α- and β-globulins of the serum proteins (228).*

In recognition of transplacental iso-immunization, "the Coombs reactions are of the greatest significance . . . to determine if the infant's red cells are coated with maternal antibodies . . . " *(229). Unfortunately, "there is no* good method of detecting anti-A or anti-B sensitivity in the infant" (230), and properly high titers must be demonstrated in the mother's serum. The antibodies (anti-A, etc.) may be eluted from the infant's tissues *(231)* by special postmortem techniques. Neonatal infections may simulate erythroblastosis foetalis (e g., syphilis, septicemia), and Capell & MacFarlane (232) have demonstrated a neonatal, fatal, febrile hemolytic anemia with remarkable renal inclusion bodies, believed to be of viral nature. However, it is safe to assume that all infants with positive Coombs tests on cord blood have erythroblastosis

Space does not permit discussion of testing procedures here. Procedures are well detailed by Levine & Wigod (233), (*Technic of Rh Testing, Diagnostic Procedures and Reagents*). Means of identification of the third order cryptagglutinoids are given by Hill, Reid & Haberman (228).

Allott & Hollman (234) found the incidence of antibodies in 147 Rh negative mothers was only 1 in 260 pregnancies. Potter & Bernstein (235) studied the blood pictures at the 1st and 8th days of life of 75 Rh positive and 74 Rh negative babies born to 149 Rh negative mothers and found no appreciable difference in the two groups. Sadowsky & Brzezenski (236) examined 324 children born of the sixth to fourteenth pregnancies to 32 Rh negative mothers with Rh positive fathers [of which about 42 per cent were probably homozygous (234)] Of these, 276 were normal offspring, 2 8 per cent were premature, 1 5 per cent stillborn, and 10 7 per cent miscarried. It was concluded *that multiple pregnancies were not themselves the cause of* sensitization. Of 4,243 deliveries in one year under observation of the Baylor University group, Hill *et al.* (228) detected antibodies in all but 24 instances (1:353). *Previous transfusion or injection of blood intramuscularly is* the commonest precedent of Rh isoimmunizations (237 to 240) in the first pregnancy.

The degree *of severity is not predictable by any measure, particularly* by titer of antibodies (234) Cord blood in normal pregnancies is often icteric, but in all with cord bilirubin which is over 4 mg. per 100 cc Mollison & Cutbush *(241) find the prognosis is severe* Sensitized mothers may bear normal children serologically susceptible to their antibodies (242, 242a, 242b).

There is no correlation between the severity of the anemia and the degree *of the subsequent central nervous system damage (243)* About *12* per cent to 15 per cent of children surviving erythroblastosis fetalis may be expected to show some neurologic evidence of damage (234, 243).

By *way of treatment* Wallerstein *(244a, 244b)* initiated exchange transfusion, infusing 250 cc by saggital sinus and exsanguinating by vein;

Wiener & Wexler (245a, 245b) followed by bleeding from the radial artery, and others by the development of special catheters to inject the umbilical vein (246) or femoral vein (247). Van Loghem *et al.* (247) have treated 160 infants by exchange and claim over-all mortality of 22.5 per cent, contrasted with 63.5 per cent by previous methods (both these figures would seem high by American standards). Massive necrosis in three infants so transfused has been reported by Rosenblatt (248). The injected citric acid is rapidly metabolized, but a rise from 2.9 to 6.9 mg. per 100 cc. after exchange transfusion has been noted (249) In truth can Mollison & Cutbush (250) exclaim "Exchange transfusion is not a trivial procedure and should therefore be reserved for cases where a single transfusion of Rh negative blood is not likely to suffice." This laudable conservatism has not marked the activity of some of our reporters, who have held the mere diagnosis of sensitization to justify exchange.

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# LABORATORY AIDS TO DIAGNOSIS AND THERAPY

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In the following summary no attempt has been made to review all of the laboratory aids which have been proposed during the past year. Bacteriological, tissue morphology, and the hematological literature dealing with blood groups will not be summarized. Attention has been reserved for what appear to be major developments or tests with a promising future for wide application.

## Adrenal Insufficiency

Renewed interest in the physiology of the adrenal cortex and the anterior pituitary has been the stimulus for the development of new and refinement of old tests for adrenal cortex functions. The older tests have been termed "tolerance tests" by Thorn and his associates (1) because they cause considerable stress and in an individual with adrenal insufficiency may precipitate a crisis sometimes with a fatal outcome. He points out that these tests should be carried out in the hospital under careful supervision Even then, their usefulness must be questioned.

The first of these is the relative ease with which hypoglycemia is induced (*a*) 2 to 3 hr. after the intravenous administration of glucose, (*b*) during a 24-hr period of fasting, and (*c*) following the administration of a small dose of insulin. This group of tests is based on the abnormally low rate of gluconeogenesis and the absence of the adrenal cortical anti-insulin effect in patients with Addison's disease (2, 3, 4). The details of the technique and interpretation of these tests have been summarized in Thorn's review (1). *Hypoglycemia data for the diagnosis of adrenal insufficiency are at best inconclusive*, and this type of test is best reserved for clinical research.

The second type of tolerance test depends on an accentuation of the electrolyte deficiency in adrenal insufficiency by restricting dietary sodium and chloride and by increasing the fluid and potassium intake. This is the Cutler-Power-Wilder test (5), a modification of the older Wilder test The test is not without danger in patients with adrenal insufficiency and requires extensive dietary preparation. Extensive laboratory work, including urine and serum sodium determinations, which are difficult in most clinical laboratories, are a desirable part of the test.

A number of screening tests have been proposed which place no excessive stress on the subject and, unlike the tolerance tests, carry no danger to the patient. One of the simplest of these is the Robinson-Kepler-Power water test (6) based on the delayed diuresis following water administration by mouth to patients with Addison's disease. A simplified procedure has been

described (1). This test may be looked upon as an index of disturbance in the adrenal cortex electrolyte factor.

One of the most interesting developments in endocrinology has been the proposal of the ACTH test by Thorn and co-workers (1, 7) as a measure of adrenocortical reserve function. Following the intramuscular injection of a single dose of pituitary adrenocorticotropic hormone (ACTH) a normal adrenal cortex is activated to secrete an increased amount of hormone. These adrenal steroids cause a progressive fall in circulating eosinophils and a rise in urinary uric acid excretion, both of which reach a maximum in 4 hr. These changes are reduced in extent or fail to occur in adrenal insufficiency (8, 9, 10).

An obvious shortcoming of the ACTH test is the shortage of the pituitary hormone preparation, which has been largely diverted to therapeutic trials in innumerable kinds of disease. When available the ACTH will of necessity be expensive, and Thorn's group has proposed an epinephrine test (11,1) as an alternative. Following the administration of 0.3 mg of epinephrine to a patient, an intact anterior pituitary gland will release sufficient ACTH to stimulate a normal adrenal cortex to increase the secretion of steroid hormones This leads to a rapid fall in circulating eosinophils as before, and the investigators have described (1, 7) a direct eosinophil count which is rapid and accurate. When ACTH is available, the two tests may be used to differentiate adrenal insufficiency secondary to pituitary insufficiency from primary adrenal cortical insufficiency. In the former the ACTH, but not the epinephrine test, may approach normal. This separation may be made more certain by repeated administration of ACTH (1).

The excretion of 17-ketosteroids in the urine may be significantly reduced in adrenal insufficiency Their determination is superfluous in either the ACTH or epinephrine tests (1). In normals the excretion of 17-ketosteroids will be elevated, although less certainly than uric acid. It is well to express the excretion of uric acid in relation to creatinine, the excretion of which is not altered. In the epinephrine test, there is no appreciable increase in uric acid excretion unless the dose of drug used be excessive.

## THYROID FUNCTION

The determination of the metabolic rate as a measure of thyroid function frequently leaves much to be desired, and there has been a continuous search for other laboratory methods which could be used to secure information about thyroid diseases Because it tends to vary inversely with thyroid activity and the basal metabolic rate, the level of serum cholesterol was long ago suggested as a diagnostic aid in thyroid disease (12, 13) Subsequently, it was pointed out (14) that although cholesterol rises in hypothyroidism and falls in hyperthyroidism, normal concentrations of cholesterol may be found in these disorders because the level to which cholesterol falls or rises therein is roughly related to the normal cholesterol concentration of the subject. The latter is influenced by the patient's heredity.

*Protein-bound serum iodine.*—The determination of the precipitable (protein precipitating reagents), protein-bound or "hormone" iodine in the blood plasma, has been gradually coming into use as a measure of the degree of thyroid activity. Two methods are in common use today. One of these (15) in its original form gave exceedingly low values, but a recent report (16) indicates that more reasonable figures are being obtained. Chaney's method (17) for blood iodine determinations appears to be the best procedure to be published so far. Modifications by other workers (18, 19) have yielded little advantage and have numerous objections. Curtis and his associates have reported many studies in which their old iodine method (20) was used; and although the relative changes in concentration are reasonable, the absolute figures are abnormally low, the lowest in the literature. Recently they have adopted a modification (21) of Chaney's method. Taurog & Chaikoff (22) have made a careful study of Chaney's method and their paper should be referred to for details The procedure is carried out in an ingenious, compact digestion and still apparatus.

The determination of serum protein-bound iodine is a procedure requiring experience and patience, but the usefulness of correct determinations warrants the attention they require. Spurious results may be obtained from the retention in the blood of organic iodine containing compounds such as gall bladder dyes, iodized oils, and iodine compounds for visualization of the urinary tract. A history regarding the possible recent administration of such preparations must be obtained.

The serum protein-bound iodine of individuals without thyroid disease usually falls between 4 0 and 8.0 μg. per 100 cc. (gamma per cent). Except in pregnancy where higher normal levels are found (23, 24), values above 8.0 occur only in hyperthyroidism. Here the serum protein-bound iodine will be from 10 to 16 and sometimes even from 20 to 30 gamma per cent. In hypothyroidism values below 3 gamma per cent are characteristic

The relation of the serum protein-bound iodine to thyroid activity and its usefulness for diagnostic purposes in thyroid disease is evident from many reports (16, 25 to 29). The apparent inadequacy of the absolute values in some of these studies (26 to 28) has been noted above.

*Radioiodine tracers.*—Iodine-tolerance tests have frequently been suggested as a means of determining the condition of the thyroid, a low urinary excretion of iodine being interpreted as meaning a high collection of iodine by the gland The radioactive isotope of iodine ($I^{131}$) and natural iodine are chemically and physiologically similar provided the former is present in amounts so small as to cause no radiation effects This has led to the use of radioiodine for numerous studies of iodine metabolism (e.g. 30, 31). The uptake of radioiodine by the thyroid and/or its excretion in the urine after the administration of tracer doses is on the way toward becoming a routine diagnostic procedure (32 to 36). The uptake by the gland is measured by placing the Geiger-Muller counter tube directly over the thyroid, and the urine excretion is easily measured in a small sample It is unfortunate that

tests with radioiodine are being concentrated in so-called isotope laboratories instead of taking their place as a new diagnostic adjunct of the x-ray or clinical laboratory.

Numerous attempts have been made to use radioiodine for locating as well as treating metastases in patients with thyroid cancer (37). The functional activity of thyroid tumors has been gauged by their collection of radioactive iodine (38, 39).

*Urine pigment excretion*.—The relation of the amount of pigment excreted in the urine to the basal metabolic rate was pointed out by Drabkin (40) many years ago. Ostow & Philo (41) confirmed this relation. Vorzimer *et al.* (42) again propose this test as a diagnostic procedure. They find the urinary pigment excretion to be a reliable measure of thyroid activity when expressed as a ratio of the absorption at a wavelength of 4,200 Å to the creatinine concentration. It is at least as good as the metabolic rate and if a routine procedure, should be more accurate and less costly.

## LIVER FUNCTION

*Gamma globulin*.—An increase in the globulin components of the blood serum has long been recognized in liver disease (43, 44, 45). It has been the basis of the nonspecific Takata-Ara (46), Weltman (47), and formol-gel (48) reactions which have been used for many years in the diagnosis of liver disease. More recently new serum reactions which depend on the stability of certain colloidal suspensions in dilute serum have been used for demonstrating liver disease. The cephalin flocculation (49), colloidal gold (50), and thymol turbidity (51) tests are of this class. Hanger and co-workers, studying the cephalin flocculation reaction (52, 53), Gray (54) and others (55) examining the mechanism of the colloidal gold reaction of blood serum, and Kunkel & Hoagland (55) and Cohen & Thompson (56) studying the thymol turbidity test in liver disease all find numerous factors which may influence the result, but they conclude that an increase in the γ-globulin appears to be the most important factor. Maclagan (57) compared all three flocculation tests with pure protein fractions and came to a similar conclusion. Fischer & Wiltner (58) propose turbidity tests of hepatic damage in which colloidal benzoin or colloidal shellac are precipitated by an increase in a globulin component and a decrease in precipitation inhibiting albumin in the serum. Electrophoretic analyses of the serum proteins in liver disease showed (59) the most characteristic alteration to be a decrease in serum albumin, which is formed in the liver (60), and a large increase in γ-globulin, which comes from extra-hepatic tissues. All of these observations suggest a direct determination of serum γ-globulin as an index of liver function.

The determination of serum γ-globulin variations by electrophoresis must remain as a reference standard since it is unsuitable for routine clinical work. Jager & Nickerson (61) have described a simple quantitative chemical method for estimating γ-globulin in human serum which has had clinical

application (62). The $\gamma$-globulin is precipitated with ammonium sulfate and determined with Weichselbaum's Biuret reagent (63). Kunkel (64) has described an even more simple method for determining $\gamma$-globulin in which the protein is precipitated with a zinc sulfate solution and the resulting turbidity read in a colorimeter. Looney & Amdur (65) suggest a modification for reducing the albumin error. Verhagen (66) has proposed a simple calcium chloride-formalin reaction with serum which correlates with the $\gamma$-globulin content. It has no advantage over the zinc sulfate method. Wuhrmann & Wunderly (67) use a cadmium reagent which primarily precipitates $\gamma$-globulin. The empirical colloidal red test (68) is probably of the same nature. When applying these simple tests to a study of patients with liver disease, Kunkel *et al.* (69) obtained results which indicate that they (64) are more useful in differentiating various types of liver involvement than the continued use of liver function tests whose mechanisms are not completely understood. For the present, the thymol turbidity and other empirical liver function tests are being widely used (70 to 74).

*Dye excretion.*—Tests which measure dye excretion have been used as an index of biliary function or hepatic reticuloendothelial activity for three decades. The 5 mg. bromsulfalein test is twice as sensitive as the rose bengal test, according to Monroe & Hopper (75). The measurement of the bromsulfalein clearance based on the slope of the curve during the fall in the plasma dye concentration after mixing is claimed (76) to be better than present methods of studying dye retention. Postoperatively, dye retention is frequently prolonged (77). Franklin (78) has described an ingenious tablet test for urinary bilirubin.

*Vitamin K test.*—Since Pohle & Stewart (79) introduced the response of depressed plasma prothrombin levels to stimulation by vitamin K derivatives as a test of liver function a number of studies (80, 81) have been made of the method Begtrup & Hansen (82) find that it is better than the common flocculation, urobilin, or galactose tolerance tests in the differential diagnosis between obstructive and parenchymatous jaundice.

*Serum esterase.*—Liver function might be measured via its rate of protein production. Fibrinogen and prothrombin are formed in the liver, and this fact for the latter is the basis of the vitamin K test (79, 82). Serum albumin is formed in the liver (60), and this protein may be reduced in amount in liver disease (59) A close correlation between the serum albumin and esterase level has been pointed out by Faber (83). A nonspecific esterase similar to the one in plasma is found in liver (84, 85) and is depressed in liver injury (84). Various observations demonstrate that serum esterase is formed in the liver (86, 87). Of the plasma proteins of liver origin, plasma esterase lends itself to accurate estimation When measured with acetylcholine as a substrate, the esterase is completely destroyed *in vivo* as well as *in vitro* by diisopropyl fluorophosphate (88, 89). Following this destruction the rate of regeneration is depressed in patients with liver disease (90, 91).

From the point of view of possible clinical usefulness the observation of Kunkel & Ward (92) that the percentage rate of regeneration is constant is most important. This means that the ordinary plasma esterase level bears a *direct relation* to the rate of esterase production by the liver, obviously measuring an important hepatic function. In no conditions other than liver disease has the serum esterase been found to be significantly depressed. In nephrosis, where there is evidence of an abnormally high rate of plasma protein production by the liver, the plasma esterase levels are very high (92).

Serum esterase determinations have not been widely adopted, possibly because most of the work has been done using acetylcholine as the substrate and the estimation required the Warburg apparatus. Now Hazard (93) has described a simple colorimetric method for serum esterase using procaine as the substrate, and his determinations in liver disease are very promising. Gomori's method (94) uses phenyl benzoate as a substrate. Goldner & Morse (95) using this method found constant values in normals but significant decreases in hepatic cirrhosis.

## Hypercholesterolemia

A continuing interest (96) in methods for the estimation of cholesterol in the plasma has yielded refinements of old procedures. There is renewed attention being given the relation of cholesterol to experimental atheromatosis and coronary sclerosis (97 to 100). The relation of the plasma cholesterol concentration to the activity of the thyroid gland has been alluded to in the section on thyroid function In attempts to produce experimental cholesterol atheromatosis, use has been made of the hypercholesterolemia of hypothyroidism by feeding antithyroid drugs along with the cholesterol (101, 102).

Most of the interest in the plasma cholesterol concentration concerns the pathogenesis of coronary artery sclerosis Essential familial hypercholesterolemia has been described by Wilkinson and co-workers (103), Boas *et al.* (104), and Stecher & Hersh (105). No association was found between the amount of cholesterol in the diet and the blood level (103). The *incidence* of coronary heart disease was higher in the patients with hypercholesterolemia (104). Morrison *et al* (106) found that a very high percentage of patients with acute coronary thrombosis have a hypercholesterolemia.

## Hematology

Studies of the technical and physiological factors in erythrocyte counting have been made by Lange & Palmer (107, 108, 109). Whitlock (110) recommends turbidometry with a colorimeter for the direct determination of erythrocyte numbers and hematocrit values. This translation from turbidometry is only possible when the red blood cells are normal in shape and volume.

The detection of erythrocyte sickling is important if diagnostic errors are to be avoided in sickle cell disease. Reducing agents are a stimulus for sickling. Various methods of deoxygenating the hemoglobin have been sug-

gested. Singer & Robin (111) recommend incubation of the blood with nonpathogenic bacteria while Murgatroyd (112) incubates with a trypanosome culture. Better tests for clinical application utilize chemical reducing agents. Daland & Castle (113) make use of ascorbic acid for this purpose. Unfortunately its action fails to distinguish between the degrees of susceptibility to sickling in active sickle cell disease and in the sickle cell trait. Itano & Pauling (114) add a fresh solution of sodium dithionite to a few drops of fresh blood which may be drawn with various anticoagulants. Thomas & Stetson (115) find that the reducing compounds hydrogen sulfide, BAL (2, 3-dimercaptopropanol), and cysteine all produce rapid and complete sickling when mixed with the blood of a patient with sickle cell disease. Glutathione, which is a less rapid reducing agent, causes sickling after a longer interval. Sickling produced by all of these compounds is rapidly reversed by exposure of the sickled cells to air.

The Hershensons (116) recommend that results of erythrocyte sedimentation tests be expressed in universally understandable terms. They suggest reporting the results in more qualitative terms, e g., negative, one plus, two plus, etc. It would seem far better to standardize the conditions of the test and try to make it more quantitative rather than less so Goldbloom *et al.* (117) consider the sedimentation test more sensitive than the flocculation tests in determining recovery from infectious hepatitis.

Bedinger & Limarzi (118) summarize the clinical interpretation of the bone marrow smear and Hargraves and his co-workers (119) describe two new types of cells in bone marrow. Huss *et al.* (120) describe a technique and the advantages of obtaining bone marrow by vertebral spinous process puncture. A somewhat different technique of spinous process puncture for obtaining bone marrow is presented by Loge (121), who, in agreement with other investigators, finds that the hemograms of marrow from the sternum and the spinous process correspond very well Rubenstein (122) describes the aspiration of bone marrow from the iliac crest and reports that the cell distribution is approximately the same as that of sternal marrow.

Suess and co-workers (123) describe an improved method for the determination and charting of the fragility of the red blood cells to hypotonic sodium chloride solution. The curves obtained are particularly useful in the hemolytic anemias and especially in the Mediterranean anemias

Allen *et al* (124) propose a protamine (combines with heparin) titration for measuring a clotting defect which is similar to but not identical with that produced by intravenous heparin administration Adequate methods

by determining the prothrombin time and heparin administration is controlled by the blood coagulation time. Voorhees and co-workers (125) describe a method for the determination of fibrin formation time based on the diffusion of thrombin into a fibrinogen solution. It appears to reflect

more accurately heparin activity *in vivo* than the conventional clotting time determination.

Hirschboeck (126) describes a new method for measuring clot retraction time which has a precise end point and uses capillary blood. The clot retraction test, a measure of coagulation time plus the interval between the end of coagulation and the beginning of clot retraction is well adapted to control of heparin therapy but is not reliable during dicumarol therapy. Rosenbaum *et al* (127) describe a test of coagulation after the addition of a specific amount of heparin to the blood *in vitro*. It has interesting possibilities.

Conley & Morse (128) find that when the prothrombin concentration of the plasma from a patient receiving dicumarol is estimated by methods which are identical except for variations in the nature or quantity of thromboplastic substance used, grossly different results may be obtained. They point out the desirability of being able to compare prothrombin levels from one laboratory with those obtained from another The importance of accurate prothrombin determinations is reviewed by Seegers & Ware (129). They also describe (130) a two stage procedure for the determination of prothrombin concentration. Quick's one stage method (131) has long been used but Olwin (132) agrees with other workers that a two stage prothrombin method provides a more accurate and safer control of prothrombin levels during dicumarol therapy. Mawson (133) uses Russell Viper venom and lecithin as the thromboplastin in a one stage test which he claims gives results comparable with the two stage prothrombin test in plasma from dicumarol treated patients. Sternberger (134) gives a further description of his "stabilized thrombin method" for the determination of prothrombin. It is tedious, but gives a direct quantitative determination of only prothrombin.

## INSTRUMENTS FOR DIAGNOSTIC TESTS

The Barkers (135) have devised a "Coagulochronometer" which is a device for automatically recording the coagulation time of whole blood. Mann (136) describes a new clinical viscometer Hartman *et al* (137) present another photoelectric oxyhemograph for continuously measuring the oxygen saturation of blood passing through the ear. The determination of sodium and potassium in biological samples has long been a tedious procedure requiring excessively large samples which are not only beyond routine clinical work, but unsuitable in most cases for clinical investigation The picture is now changing since the introduction during the past several years of flame photometers with photo tubes for measurement. One instrument is manufactured by the Perkin-Elmer Co., Glenbrook, Conn., the other is the Beckman flame spectrophotometer (a combination of the model D. U. Beckman spectrophotometer and the Beckman flame photometer attachment) manufactured by National Technical Laboratories, South Pasadena, *California*. The latter is a more useful albeit more expensive instrument. Among others Hald (138), Overman & Davis (139), Marinis *et al.* (140), and Mosher *et al.*

(141) have had occasion to use and have recently reported their experiences with these photometric apparatuses. The literature and the personal experience of this author indicate that the Beckman equipment gives the better results of the two at the present time. The novice should not expect perfection from the determination of sodium and potassium by flame photometry. An expert technician who is operating the machine regularly and checking his results at frequent intervals can obtain excellent results with much smaller samples and a modicum of the time required by older methods. Another laboratory "gadget" applied to serum sodium estimation is an electrical conductivity assembly (142). It is probably less accurate for this purpose than the flame photometer, is expensive equipment, and just as likely to get out of kilter.

With the development of improved analytical methods, there are many attempts to apply sodium and potassium determinations to diagnostic tests as well as to studies in clinical physiology. Sodium excretion is decreased in cirrhosis of the liver (143). A salt tolerance test for adrenal cortical hyperfunction (144) requires sodium determinations. Potassium deficiencies are being noted (145, 146).

## Miscellaneous Urine and Blood Tests

The concentrating ability of the kidney has long been useful in determining the extent of renal damage. Taylor's comparison (147) of Addis' regime of simple abstention from fluid and watery foods for 24 hr. with the posterior pituitary extract test indicates the desirability of the former. The test specimen may also be used to count the formed elements (Addis Count). Giles (148) reports the Addis Count to be very useful in determining the prognosis of acute nephritis in childhood.

Hiller and co-workers (149) describe an excellent method for the determination of protein in urine by the biuret method. Dittebrandt (150) uses the biuret reagent for the determination of spinal fluid protein, while Kilbrick (151) and Cohn & Wolfson (152) apply it to the determination of serum globulin and albumin. Chow *et al.* (153) determine serum albumin by means of the precipitin reaction

Screening (154) and bedside (155) methods for blood sugar have been described. Colorimetric methods for serum calcium (156), sodium (157), chloride (158), and amylase (159) appear promising.

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# THERAPEUTICS AND TOXICOLOGY[1]

By William T. Salter

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At the present date, a little over a generation from Weir Mitchell's "era" of therapeutic nihilism (1), the clinics and the literature abound in new therapeutic agents. It is obvious that many of these recent acquisitions are not yet officially recognized, i.e., by the U. S. Pharmacopeia or by the National *Formulary*. *By the time some of them become so well substantiated as to be* included in the official compendia, they will no longer be known as recent advances. Therefore, in this article, only tentative appraisals and descriptions can be given. Doubtless time will dampen many present enthusiasms, but only through continuous critical interest can the final story of each drug be assessed.

With this caution in mind, it may be noted that an extraordinary feature of recent progress is a marked tendency toward genuine or apparent specificity. If specificity be accepted as important evidence of therapeutic progress, the long list of new drugs which are "anti-" 's is impressive Whether or not these survive, their present existence indicates an ever-increasing interest in the relief of disease along mechanistic lines, rather than through blind empiricism. If the discussion here is superficial, it is due in part to limitations of space, but also in part to the superficial state of knowledge concerning the pathogenesis of many disease states. Indeed, in several instances the drug itself supplies fundamental clues as to pathogenesis. This fact will be apparent from scrutiny of the arbitrarily selected list of agents to be discussed: antianemia vitamins, antithyroid substances, antibiotics, adrenocortical substances, anticoagulants, antihistaminics, antacids, adrenergic-blocking and related agents, central nervous system depressants and anti-spastic agents, diuretics, anti-hypertension substances, and drugs useful in acute renal failure

## Antianemia Vitamins

*Vitamin $B_{12}$* —A definitive report by West (2), shortly before his untimely death, constituted a milestone in progress in the study of anemia and nutrition. The finding by Shorb (3) that the effects of liver extracts upon the growth of *Lactobacillus lactis Dorner* were correlated with their individual potencies in *pernicious anemia led to the isolation of vitamin $B_{12}$ in the form* of reddish crystals by Rickes *et al* (4) and by Smith (5). The material contains cobalt, phosphorous and nitrogen, but no sulfur Doses as low as 1 µg. daily, administered parenterally, will produce a satisfactory response in pernicious anemia (6, 7) This new vitamin, unlike folic acid, has a strikingly

[1] This review covers the period approximately from January, 1948 to January, 1950.

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toxic) is popular. In animals, at least, and probably in man there are more potent derivatives than the 6-n-propyl, but as yet no significant body of clinical evidence is available on this point. That patients with mild thyrotoxicosis may be treated over long periods with goitrogenic drugs alone has been shown in several clinics, e.g., by Astwood (13) and by Danowski *et al.* (14). For example, the latter group treated 118 thyrotoxic patients with thiourea (15 to 280 mg. daily), often supplemented with strong solution of iodine (5 to 15 minims daily) Most of the 89 thyrotoxic patients who were followed from six months to over two years were well controlled; but relatively few became entirely symptom-free and the majority relapsed when the medication was reduced. If anything, exophthalmos regressed under such therapy; whereas after surgery there is a distinct tendency toward increased exophthalmos. An occasional patient experienced nausea at the start of therapy; but this receded without interruption of the medication. Halitosis was prominent in many of the patients.

In contrast to the constant supervision required by such ambulatory patients, long series of patients have been reported by surgeons like Bartels (15) in which the operative mortality is about one in 1,300. The reduced operative hazard and the relatively short postoperative convalescence which these patients enjoyed were due in large part to the preoperative use of propyl-thiouracil supplemented by iodide. About 2 per cent of patients receiving propyl-thiouracil show untoward reactions, chiefly leukopenic, but frank agranulocytosis is extremely rare. The period required for maximal antithyroid effect is uncertain in the individual case; but this wait of two to six weeks usually can be managed while the patient is at home. Surgical complications and the number of recurrences vary, of course, with the skill and zeal of the individual surgeon At the present time, however, it is difficult to offer any broad statement which will allow a choice between these two therapeutic approaches.

Each method now is hard pressed by the use of radioiodide, especially with the eight-day isotope $I^{131}$ At the 1949 meeting of the American Goiter Society, the late Mayo Soley predicted that within 10 years nearly all cases of Graves' disease would be treated with radioiodide alone. The regimen followed varies with each clinic, but all use some method of estimating the probable intensity and totality of beta-rays to which the thyroid tissue will be exposed. This can be done either by estimating by palpation the probable weight of the goiter or by using a small test dose as a guide to the avidity of the glandular tissue for iodide. In general, the initial dose of $I^{131}$ is frequently around 5 millicuries, given in a glass of water. There is no odor or taste. For two or three days there may or may not be some evidence of mild thyroiditis, and a slight increase in circulating thyroid hormone may occasionally precipitate cardiac irregularity. Such complications are rarely serious. The maximal depressant or destructive effect on the goiter is attained in about four weeks, when therapy may be repeated if necessary. Occasionally several

beneficial effect upon the early symptoms of combined sclerosis. Vibratory sense, however, shows least improvement (8). When ingested, $B_{12}$ is ineffective unless given with gastric juice. Moreover the oral dosage is some 40-fold the parenteral and erratically assimilated. Bethell (9) has found that the *response to* $B_{12}$ *is inhibited by folic acid antagonists.* In the pernicious anemia of pregnancy and in the acute megaloblastic anemia of infancy, folic acid is beneficial whereas $B_{12}$ is not. Thymine (5-methyl uracil) in large doses is intermediate in its reaction, because it can improve the blood picture in pernicious anemia and in sprue, but not the neurological symptoms, which may possibly be aggravated. A theoretical hypothesis now under study is that folic acid acts as a coenzyme to expedite the formation of thymine, which is then converted to thymidine (the desoxyriboside of thymine) by the catalytic effect of $B_{12}$. Cobaltous chloride has no effect in pernicious anemia, although it can produce polycythemia in animals. Possibly its physiologic role is analogous to that of iron in cytochrome.

At the moment the cost of producing pure vitamin $B_{12}$ is many times that for extracts containing about 50 per cent of the vitamin. Therefore it would be convenient if partially purified preparations could be assayed for their $B_{12}$ content. Unfortunately at the time of writing no such procedure can be agreed upon; although there is an undoubted correlation between the clinical efficacy of liver extracts and their influence on bacterial growth. Exceptions to this statement, however, exist which are both positive and negative arithmetically; and certain pure substances are known to give a false positive, simulating $B_{12}$. Consequently the present U. S. P. unitage, based on human responses, is being retained until the technical difficulties of biological assay have been resolved.

These therapeutic achievements are paving the way toward a better understanding of nutrition, particularly in relation to the maturation of immature cells Already a vitamin $B_{14}$ is under study. Nevertheless the interrelation of the pterins, of folic acid, and of vitamin $B_{12}$ remains obscure.

With respect to the treatment of neoplasms by antagonists of folic acid, Rhoads (10) has reported that whereas aminopterin shows little specificity for malignant cells, there does seem to be some advantage in the use of $\alpha$-methopterin, i.e., 4-amino-$N^{10}$-methyl pteroylglutamic acid (11, 12) in leukemia. For example, in chronic myeloid leukemia a fall in leukocyte count can be induced with high regularity, and frequently with decrease in size of spleen and liver. Thus one more chemical agent becomes available as a temporary aid in the therapy of cancer or leukemia.

## Antithyroid Substances

The pendulum of clinical opinion concerning the therapy of thyrotoxicosis continues to oscillate, but its swings are less violent. In the United States, 6-n-propyl-thiouracil has practically supplanted other drugs in practice; although in Europe the methyl derivative (which is more effective but more

*disturbance* (e.g., *ataxia*). After prolonged use (several weeks to several months), however, its effect upon locomotor equilibrium and upon hearing is not very different from that of the older drug. Because streptomycin-fastness limits the duration of therapy for acute gram-negative infections, dihydrostreptomycin does have a certain advantage, although slight.

*In tuberculosis, results with streptomycin are approaching a stage where* some evaluation can be made. For instance, the Medical Advisory Committee of the Connecticut State Tuberculosis Commission (22) suggests its use in the following types of case: disseminated miliary and meningeal infection, recent acute exudative lung involvement; subacute pulmonary infection with fine nodular distribution; as a prelude to thoracoplasty; in lung lesions characterized by ulceration and thin-walled cavities; in fluctuating infections, and for chronic sinuses or superficial tuberculous abscesses. The duration of trial should rarely exceed 90 days, and the dosage should be approximately 0 01 gm. daily per pound of body weight. It should be given in 2 or 3 divided doses; no single dose should exceed 0.75 or 1 0 gm. In tuberculous meningitis, Lincoln *et al* (23) have combined with streptomycin the sulfone, thiazosulfone (Promizole) which can be continued for years (24).

Aureomycin, obtained as a yellow crystalline hydrochloride from *Streptomyces aureofaciens*, is of special interest because of its efficacy over a wide range of infecting organisms. It acts both on gram-positive and gram-negative bacilli of many varieties, also upon the Rickettsiae of Rocky Mountain spotted fever and upon the virus of lymphogranuloma venereum Long's associates (25) used 6 to 12 oral doses daily totalling 10 to 60 mg. per kg. When given intramuscularly (at a dosage of 3 mg per kg daily), it produced moderate focal irritation. Striking results were obtained in urinary infections of *Bacillus coli aerogenes* and *Streptococcus faecalis* In chronic brucellosis (*Brucella suis*) the fever abated within three days Five patients with Rocky Mountain spotted fever became asymptomatic in one to three days. Wright *et al* (26) treated 25 cases of lymphogranuloma venereum by intramuscular injections of 10 to 40 mg. daily. Within four days the buboes declined in size; indeed after two days aspiration revealed that inclusion and elementary bodies became pleomorphic and stained poorly. Likewise, lymphogranulomatous proctitis, with or without ulceration, reverted to normal rectal mucosa. There is some evidence, also, that aureomycin may be effective in atypical virus pneumonia (27); but its status as a routine therapeutic agent in this condition has not yet been validated satisfactorily

Chloromycetin, or chloramphenicol, isolated by Burkholder *et al.* (20, 28) from a soil actinomycete originating near Caracas, Venezuela, has proved

duration of fever was 18 days. Treatment could be completed by giving orally 6 gm of the drug in 24 hr. In 15 cases of Rocky Mountain spotted fever, Smadel's associates (30) gave tablets orally (each 0 25 gm ) The initial dose

such treatments are required. About 10 per cent of the energy radiated from $I^{131}$ is gamma, but the chief importance of this is its convenience in estimating the fixation of isotope in the gland.

If more enthusiastic dosage be used, the danger of hypothyroidism increases. At present some 6 per cent of such patients show temporary evidence of hypothyroidism; but only 1 per cent suffers permanent myxedema. Of course, this is readily relieved by thyroid substitution therapy.

At present, radioiodide is not used in nontoxic nodular goiter. Even in toxic nodular goiter its use is questioned except when combined with early surgery, and largely for diagnostic purposes. This question is intimately concerned with the problem of precancerous and cancerous lesions of the thyroid. In thyroid cancer the results of Seidlin (16), Rawson (17), Dobyns (18), and others (19) are exciting, but it is too early to evaluate the ultimate value of this tool in cancer therapy.

## Antibiotics

Among the many antibiotic agents which have been tested by laboratory workers, e.g., Burkholder (20), the outstanding preparations which have attained clinical recognition to date are procaine-penicillin, dihydrostreptomycin, aureomycin, chloramphenicol, and bacitracin.

Procaine-penicillin is a crystalline substance obtained by combining one molecule of procaine base with one molecule of penicillin; the resulting complex contains over 58 per cent of penicillin, nine-tenths of it as penicillin G. The material is available both in aqueous and oily media, and there is little to choose between them. Both the aqueous and sesame-oil suspensions tend to sediment into a cake which requires vigorous shaking to suspend it again, and some crystals form masses which clog the 21-gauge needle employed for intragluteal injection. Boger *et al.* (21) showed that 18 of 23 patients recovered from bacterial pneumonia without complications after a single injection of procaine-penicillin G in oil. Formerly such effects might have been attributed solely to the prolonged action of this form of medication. It appears true, however, that pneumococcus pneumonia will yield to one or two injections daily of 300,000 units of old penicillin In other words, the continuous maintenance of a significant level of circulating antibiotic may not always be essential. Two features appear to contribute to this paradoxical effect· first, the initial high surge of antibiotic into the blood serves to prime the tissue fluid and lymph with drug which persists after the plasma level declines; and, secondly, the bacteria suffer a continuing effect from earlier exposure to high concentrations of penicillin. In brief, former evaluation of the significance of plasma concentration must be modified, at least for the pneumococcus

Dihydrostreptomycin has been introduced in an effort to eliminate some of the toxic effects of streptomycin (N-methyl-L-glucosamido-streptosido-streptidine). In general, it appears to be equally effective clinically. Moreover, when used for only a fortnight, it is less likely to produce vestibular

disturbance (e g., ataxia). After prolonged use (several weeks to several months), however, its effect upon locomotor equilibrium and upon hearing is not very different from that of the older drug. Because streptomycin-fastness limits the duration of therapy for acute gram-negative infections, dihydrostreptomycin does have a certain advantage, although slight.

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[illegible]

6 gm. of the drug in 24 hr. In 15 cases of Rocky Mountain spotted fever, Smadel's associates (30) gave tablets orally (each 0 25 gm.) The initial dose

for adults was about 75 mg. per kg.; *thereafter at three-hourly intervals* (day and night) 0.5 gm. was given until the temperature remained normal for 24 hr. Usually the patient was afebrile on the third day.

In typhoid fever, Smadel *et al.* (31) showed that the *Eberthella typhosa* could be suppressed rapidly by oral administration of the drug. Ten patients so treated showed an average febrile course of 3.5 days; whereas for the 8 controls, fever lasted 35 days on the average, with one death. These observations have been confirmed by McDermott (32) and others. Chloramphenicol has now been studied in several other series of patients (33, 34). If relapses are to be avoided, the drug should be continued (in divided doses totalling 3 gm. daily) for more than eight days. Therapy after 14 days is superfluous.

Bacitracin continues to serve as a local antibiotic. It is too toxic for systemic use.

## Adrenocortical Substances

*Compound E.*—The starting culmination of years of patient research by Kendall and his associates (35) has been the demonstration by Hench (36) that large doses of cortisone, or Compound E (i.e., 11-dehydro, 17-hydroxycorticosterone), produce a dramatic relief of certain rheumatoid disturbances and may be life-saving in lupus erythematosus. The effect also is produced by the adrenocorticotrophic hormone (ACTH) of the pituitary, presumably by the indirect production of natural cortical steroids. The mechanism of action in arthritis is unknown. At least it is clear that in the patients suffering from rheumatoid arthritis no evidence exists of hypocorticism as found in early Addison's disease. Therefore, the response to cortisone must be regarded as pharmacological rather than as a simple replacement therapy compensating for an endocrine deficiency. Even repeated and continuous dosage with epinephrine, as demonstrated by Thorn (37), may produce relief by increasing the patient's adrenocortical activity. Many speculations are rampant but remain unanswered as to the therapeutic implications of the present observations. For instance, does the cortisone merely dissolve inflammatory cells and alter the permeability of cell membranes so that the inflammatory reaction remains in abeyance? Is the response due to Compound E or to some metabolic degradation product? What is the possibility that such patients will be forced to exchange Cushing's syndrome for their arthritis?

At the [illegible] therefore, the status of this treatment is distinctly in the stage of [illegible] to 300 mg. [illegible] after 2 or 3 days of therapy, it disappears just as rapidly when medication is stopped. Much of the relief is due to the unlimbering of protective muscle spasm, although disappearance of swelling and warmth of the affected periarticular soft tissues is evident. Obviously long-standing cases with bony deformity and muscular atrophy cannot hope for great improvement. It has been estimated that the cost of treating a favorable patient at present is about $180,000 per annum. Moreover, all the world's possible sources of

starting material (e g., slaughter-house glands, ox bile, species of Strophanthus, Mexican yams) at present could supply only one-sixth of the probable demand in the United States. The available supplies of Compound E are pitifully meager in proportion to the problem, and a special committee has been constituted to consign the limited supply for investigative purposes.

## ANTICOAGULANTS

Accumulating experience with heparin and dicumarol has demonstrated abundantly their efficacy in the prevention and treatment of various kinds of thrombosis. The incidence of untoward effects, however, is sufficiently large to indicate that these drugs should be used only in hospitals with ample laboratory facilities. If daily determinations of prothrombin can be made, the relatively inexpensive, orally effective dicumarol meets most requirements, excepting those of an acute emergency. Indeed, the gradual onset and slow recovery of prothrombin deficiency under dicumarol are advantageous properties in skilled hands. Because heparin in doses of 50 mg. must be injected every 4 hr., and because one day's therapy costs $9 (against a few cents for dicumarol), its usefulness on a large scale will be limited

From the work of Jorpes (38) it is known that heparin is a mucopolysaccharide chemically related to chondroitin sulfuric acid Moreover, its anticoagulant effect is connected with the presence of a polysaccharide moiety of high molecular weight. If such a molecule could be manufactured synthetically at low cost, the usefulness of such a "heparinoid" might be considerable. Sources of high-molecular-weight carbohydrates are found in nature, notably in agar-agar. Therefore, it is not surprising that Seifter and his associates (39) have been able to develop derivatives of agaric acid which, although only about one-tenth as potent as heparin, are much cheaper. These serve well in surgical and physiological experiments on animals If administered in too high a dosage, they will block the kidney and until further clinical trial is completed, their status must remain *sub judice* The action of such material, however, is quite similar to that of heparin as described by Loewe (40). He showed that heparin simultaneously acts as antiprothrombin, as antithrombin, and as an inhibitor of platelet agglutination. In the clinic its antagonist protamine is rarely needed (50 mg intravenously), because of the brief duration of heparin activity. When dicumarol is used, the initial dose of 300 mg should be supplemented by daily doses of 150 to 200 mg. only when the blood prothrombin concentration is higher than 20 per cent of normal Excessive bleeding usually can be controlled by repeated transfusions of fresh blood, supplemented by intravenous vitamin K (e g., 60 mg. of menadione) Excessive capillary fragility (by Rumpel's stasis test) is also a warning sign in the use of dicumarol.

The use of these drugs, under constant vigilance, may be justified in cardiovascular disease. There is no question of their use in acute embolism or thrombosis of peripheral arteries, as described by Allen (41). In postoperative prophylaxis the results of Allen *et al.* (42) in some 1,500 cases (with

expected fatal pulmonary embolism in 86) showed only one death from pulmonary embolism. In coronary thrombosis Peters *et al.* (43) observed a mortality of 26 per cent in 86 cases not treated with dicumarol, as contrasted with 11 per cent among 110 cases treated with this drug. Corresponding percentages for clinical embolism were 15.1 vs. 0.9. Such data suggest strongly that carefully controlled prophylactic therapy is worth while. Obviously, time and expense are limiting factors in such a program.

*Hyaluronidase.*—Related chemically to heparin is hyaluronic acid. This material is present in the primitive mesenchyme, and as pointed out by Chambers & Zweifach (44) is an important constituent of the intercellular cement substance of adult tissues. The penetration of extraneous material through this matrix is necessarily slow, but certain pathogenic organisms dissolve it with the help of an enzyme known as "hyaluronidase." Important studies of this enzyme have been made by Meyer (45) Chain & Duthie (46) concluded that hyaluronidase and the "spreading factor" are identical.

Physicians are now attempting to apply in therapy the trick taught them by the pathogens (47). For instance, Hechter *et al.* (48) found that hyaluronidase facilitates the absorption of fluid from tissue spaces. In infants injected subcutaneously with 30 ml of plasma, the resulting swelling usually requires 6 to 24 hr. to recede; but if hyaluronidase is added to the fluid, absorption occurs within an hour and with less discomfort. The mechanism of action of the hyaluronidase has been reviewed in detail by Duran-Reynals (49, 50), and others (51). Especially in pediatrics, it seems possible that this material may have an important application in the administration of nutrient fluids. The same applies to adult patients in whom attempts at the intravenous administration of fluids have been in vain.

Apart from its direct therapeutic use, hyaluronidase has become implicated in problems of fertility, because the ovum while in the fallopian tubes is covered with follicular cells embedded in a viscous jelly (52). This matrix material, composed in part of hyaluronic acid, is dispersed by hyaluronidase, obtained from sperm (53) A viscosimetric method for determining this enzyme in human sperm has been described by Bergenstal & Scott (54). The activity in homogenized whole semen is highest at or shortly after ejaculation.

## ANTIHISTAMINICS.

Since 1942 when Halpern (55) demonstrated antiallergic effects in man through the use of Antergan, new antihistaminic drugs have been appearing apace. As described by Loew (56), in the guinea-pig such drugs may safely antagonize up to 1,500 lethal doses of histamine and in sensitized animals, may protect against several lethal doses of serum. Unlike epinephrine, which is perhaps the best antidote available for acute overdosage with histamine, these drugs do not provoke pharmacologic effects which oppose those of histamine. They do not check the flow of gastric juice classically produced

by histamine. They do not elicit any great relaxation of bronchial or intestinal musculature; but rather, they operate as blocking agents, much as atropine blocks the action of acetylcholine.

As indicated by Dragstedt (57), the role of histamine in human allergy is by no means clear. Therefore, the transference of laboratory assays involving histamine to clinical problems has been difficult, apart from species variation. A large number of pharmaceutical organizations have advertised their particular product as superior to Benadryl (58) and Pyribenzamine (59) which were introduced in 1945. Nevertheless, harassed practitioners continue to be troubled by complaints by patients of somnolence, giddiness, or mild confusion.

Recently, Loveless & Dworin (60) have reviewed the effectiveness of 11 such drugs in the treatment of allergy. In general, about two-thirds of the patients experienced some benefit. The highest values were 82 per cent for urticaria and angioedema, 73 per cent for extrinsic rhinitis, and 65 and 62 and 62 per cent for contact and atopic dermatitis, respectively. In general, about 29 per cent of patients experienced untoward reactions, with sedation, gastrointestinal disturbance, and confusion predominating. Of 11 antihistaminic agents involved in about 13,000 tests the three leading compounds in the judgment of these authors were Trimeton, Pyribenzamine, and Thephorin The present writer is somewhat skeptical of the application of such data in the individual case because patients appear to vary so much qualitatively. Each patient is a new testing material and the drug that benefits one may make the next individual ill. This is no argument, however, against the use of such drugs, if proper precautions are taken The patient should be warned against automobile driving while in a possible dream state produced by such a drug, or even against travelling alone in crowded railroad stations. A special instance is the precipitation of convulsive seizures by the antihistaminics, as described by Churchill & Gamon (61). This is particularly important in epileptic children.

A recent application of these drugs is in the control of vomiting, which may be demonstrated in dogs about to be treated with apomorphine. In the pernicious vomiting of pregnancy, likewise, these drugs offer one more therapeutic maneuver which may be tried.

A special case is the use of Dramamine in sea-sickness. The report of Gay & Carliner (62) on the effect of dimenhydrinate in motion sickness deserves special comment. In the Allergy Clinic of the Johns Hopkins Hospital, β-dimethylamino ethyl benzohydryl ether, 8-chlorotheophyllinate was administered to a pregnant woman who suffered from urticaria and car

carrying 13,660 soldiers to Bremerhaven, Germany late in 1948. Part of the personnel was treated with 100 mg. every 5 hr and before retiring, and a

striking relief was observed. Likewise, Strickland & Hahn (63) studied the influence of this drug on air sickness and found that with Dramamine 28 per cent were airsick whereas with a placebo 56 per cent were ill. Commenting upon these results, Tyler (64) suggests that 0.6 mg. hyoscine has been shown to give a similar degree of protection. In the present general enthusiasm for this drug the possibility of untoward side-effects may be forgotten. Certain individuals, however, already have noted drowsy dream-like states following its use. Probably a few individuals will find it difficult to choose between the dizziness of sea-sickness and the giddiness of drug origin. Therefore, each individual should be tested carefully both as to qualitative and quantitative reaction, especially if he is to be ambulatory and alone.

Another special use of an antihistaminic is the topical use, in ointment form, described by Strauss (65) for bee stings. Although the primary toxic agent secreted is almost certainly not formic acid, but rather a complex mixture containing a basic alkaloid (66), the relief of discomfort and prevention of local inflammatory or allergic reaction is striking if topical therapy is applied early. In his trials, Strauss used Thephorin ointment, i.e., 2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene hydrogen tartrate.

Numerous new antihistaminic agents are now on trial. For instance, Halpern (67) has recently reported on certain phenothiazine derivatives, notably "Phenergan" (i.e., N-dimethylamino-2-propyl-1-phenothiazine or or 3277 R.P.). In clinical trials it relieves serum sickness, urticaria, angioneurotic edema, acute hay fever and allergic purpera. In eczema it is of no value; and of little value in asthma, migraine or pruritis. An interesting feature of this drug is that it prevents the production of experimental acute pulmonary edema (produced by epinephrine or poison gas) and orthostatic albuminuria. It is thought to act chiefly by preserving normal capillary permeability.

It is too early to evaluate scientifically the present vogue for antihistaminic treatment or prophylaxis in the common cold. The author is highly skeptical except in those cases in which the coryza clearly provokes a latent allergy.

## Antacids

The problem of hyperacidity in peptic ulcer is always with us and with it the choice of antacid agents. The evaluation of their usefulness is complicated by many extraneous factors. For instance, Batterman & Ehrenfeld (68) have presented evidence that tobacco smoking thwarts the beneficial action of antacids. Conversely, Ivy and his associates (69) present evidence that enterogastrone injections (three or six times per week for one year) prevented the usual hypercontinuous secretion. Careful comparative studies of the many antacid reagents are few and, therefore, the studies of Batterman & Ehrenfeld (70) are of special interest. They conclude that alkaline powders, magnesium trisilicate, nonreactive aluminum hydroxide gels (by themselves) and aluminum phosphate gel are unsatisfactory for the long-

continued treatment of the ulcer patient. The liquid gel or tablet forms of reactive aluminum hydroxide preparations, together with sodium aluminum silicate, appeared to be equal in effectiveness, although varying in constipating effects.

Unfortunately, comparative data are not available on two newer antacid agents, i.e., *protein hydrolysates and resins*. An evaluation of the antacid activity of a protein hydrolysate was made by Rossien, who found optimal effects one hour after doses of about 40 gm. (71). After this time it tended to stimulate acid-formation unless another dose were given. An ingenious method of acid removal has been applied in the form of anion-exchange resins by Kraemer & Lehman (72). Using a polyamine-formaldehyde resin known as Amberlite IR-4, in fine-mesh particle size, they treated 36 cases of peptic ulcer, with satisfactory progress. Apart from a sandy taste and odor, this highly effective acid remover appeared to have no annoying side effects.

## Adrenergic-Blocking and Related Agents

The pure pharmacologists have been delighted with the advent of three modern adrenergic-blocking agents, i.e., dibenamine, priscol(ine), and tetraethylammonium chloride. In the clinic, however, these have not proved to be without danger; and their status as therapeutic agents is still under consideration. In recent months and years certain practical information has accumulated both as to their therapeutic usefulness and toxicological pitfalls.

*Dibenamine*.—The properties of N, N-dibenzyl-$\beta$-chloro-ethylamine have been described in detail by Nickerson & Goodman (73). It is chemically related to the nitrogen mustards, and shares their local irritant properties and cerebral stimulation. Although it does not destroy epinephrine either *in vivo* or *in vitro*, it shows marked adrenolytic and sympatholytic action. It evidently acts upon the ultimate effector cells and thus blocks both the excitatory action of epinephrine and also of norepinephrine (arterenol, formerly confounded with the hypothetical Sympathin E). Like ergotamine, this drug produces a reversal in arterial pressure response after epinephrine. Furthermore, the results of sympathetic nerve stimulation are blocked. Because its enteral absorption is erratic, it is ordinarily given intravenously in dosage from 4 to 6 mg. per kilogram of body weight. It must be given slowly lest convulsions be provoked. The maximal activity occurs within the first day after injection, but significant sympatholytic effects may be detected for a day or two thereafter.

In a cat so treated, the barking of a dog will cause no dilatation of the pupil. In high-strung patients, a situation which is normally exciting causes little change in pulse or arterial pressure. Naturally the results in essential hypertension have been tried. One such series was reported by Haimovici & Medinets (74). They administered 5 mg. per kilo of dibenamine hydrochloride intravenously in an infusion of about 400 ml. of normal saline or 5 per cent glucose. The time of administration lasted well over an hour and the

vein was then flushed with several ounces of fluid to prevent thrombosis. No dose over 500 mg. was used. In 30 tests on 18 control subjects, the mean blood pressure changed only from 124/73 mm. Hg (before) to 122/69 (after treatment). The response of hypertensive patients varied. One group of six with arteriosclerotic heart disease showed pressures of 177/81 before and 170/79 afterwards, i.e., no significant change. A second group of seven patients with essential hypertension in the malignant phase likewise showed no significant fall in pressure. A third group of seven patients with essential hypertension (1 benign, 6 malignant) showed striking responses to the drug. In 17 tests on these last-named patients, the mean pressures were 180/112 before administration and 132/86 afterwards. The decline in pressure was maximal about 40 min. after treatment, although in two instances it was delayed further The effect wore off in 1 to 3 days; but if treatment were repeated soon, the second response tended to exceed the first. It has been suggested that such patients make good subjects for sympathectomy operations, as described by Smithwick (75).

Unless confined to bed for 12 hr. these patients are prone to sudden vasomotor collapse (postural hypotonus). A few suffered from venous pain during the infusion or from subsequent phlebothrombosis. Several complained of dry mouth, drowsiness, nausea and mental confusion Obviously, the use of this drug in patients at home presents difficulties.

*Tetraethylammonium chloride.*—TEAC (Etamon Chloride) blocks the autonomic ganglia, as shown by Acheson & Moe (76). Thus impulses travelling over preganglionic fibers fail to reach postganglionic fibers innervating such viscera as the heart, stomach, and intestine. It acts both on parasympathetic and sympathetic ganglia so that its actions are diffuse It is supplied in 10 per cent aqueous solution. Because of the danger of sudden respiratory paralysis from rapid intravenous administration, it is best administered intramuscularly in dosage less than 20 mg. per kg, i.e, 5 or 6 ml. of the solution in each buttock. If given intravenously, the dose should not exceed 7 mg. per kg. One or two daily injections may be given because the effect lasts only a few hours.

The drug has been tried in peripheral vascular disease (i.e, Buerger's disease, Raynaud's disease, thrombophlebitis, and causalgia) The danger of postural hypotension lasts for at least an hour and the patient should lie down during this time. Loss of micturition and defecation may last longer. If the effects are excessive, obviously epinephrine or neostigmine may be used to counteract them.

The use of TEAC in clinical hypertension was reported by Lyons *et al.* (77), involving 437 patients who received about 40 mg of the drug intravenously Usually the blood pressure declined significantly within 5 min. and remained so for over 10 min During another half hour or more, even though the recumbent pressure remained within normal limits, the patient was likely to show postural hypotension The pulse pressure was low and the peripheral vascular flow increased. The individual variation among these

patients was rather wide. As might be anticipated, this drug can be used to predict the effects of splanchnicectomy. Moreover, its effect on arterial pressure is largely lost after splanchnicectomy. It would seem that it should be used only under close clinical supervision.

Several gastro-enterological specialists have recently adopted TEAC, chiefly as a research tool. Thus Brown, Posey & Gambill (78) observed that complete cessation of gastric motility and a marked reduction in acidity occurred for about 40 min after intravenous administration, and up to 3 hr. after intramuscular injection. The quaternary ammonium compound was also injected intravenously (in doses of 0.3 to 0.5 gm.) by Dodds *et al.* (79), who observed a rapid, uniform cessation of both gastric and intestinal peristalsis, with loss of gastric tone similar to that caused by vagotomy. Among 20 normal subjects, 45 per cent showed delayed gastric emptying. Somewhat higher doses, i.e., up to 600 mg. intravenously, were found by Zweig, Steigmann & Meyer (80) to abolish all gastric motility within 5 min. and to decrease by 70 per cent the gastric response to a continuous intravenous infusion of histamine phosphate.

Although the drug does not block painful stimuli from the gut carried by visceral afferent nerves, often it does afford temporarily relief from enteric pain. Probably this is because its effect on the bowel and gastric activities exceeds that of atropine and of epinephrine. As pointed out by Neligh *et al.* (81), side effects (e.g., mydriasis, dry mouth, orthostatic hypotension) prevent continued use of the drug Nevertheless, Cayer, Little & Yeagley (82) have used TEAC in the treatment of 12 patients with active duodenal ulcers. Intramuscular injections were given thrice daily, up to a single dose of 600 mg. In these "bed" patients the pain due to ulcer was uniformly relieved, even though no alteration of gastrointestinal motility could be demonstrated on x-ray examination. In patients suffering from nocturnal pain, the resulting 6 hours of comfort were particularly gratifying. Besides mild local soreness and hypotension, the outstanding side-reaction was eyelid ptosis for half an hour.

Meanwhile, studies of the older autonomic blocking agents goes forward. For instance, Taliaferro, Adams & Haag (83) have commented on the use of the adrenolytic benzodioxan drugs as diagnostic agents in suspected pheochromocytoma, as suggested by Goldenberg, Snyder & Aranow (84). The latter investigators reported that the Fourneau compounds 933F (i.e., 2-[1-piperidylmethyl]-1,4-benzodioxan) and 1164F (i.e., 2,4-dimethyl piperidyl methyl-benzodioxan) on intravenous injection caused a fall in arterial pressure when raised by such tumors. Likewise, Spear & Griswold (85) found that dibenamine depressed the hypertension in one case of pheochromocytoma Other drugs cause a rise in pressure, e g., histamine, TEAC, and methacholine bromide (mecholyl bromide) In a case of renal hypertension, Taliaferro *et al* found the arterial pressure to fall from 200/165 mm. Hg to 120/98 mm Hg within a few minutes after the intravenous injection of 16.8 mg (10 mg. per sq. m ) of benzodioxan in 1 per cent aqueous solution.

Dibenamine and histamine produced trivial changes in arterial pressure. TEAC however, in an intravenous dose of 400 mg. produced a profound hypotension. This last result is characteristic of essential or renal hypertension, in contrast with the results in pheochromocytoma demonstrated by LaDue, Murison & Pack (86). Evidently a depressor *response after benzodioxan* does not necessarily indicate the presence of pheochromocytoma. Such drugs can be useful in preoperative treatment, however. Thus Grimson *et al.* (87) have used C 7337, i.e., 2(N, para-tolyl-N[m-hydroxyphenol]-aminoethyl)-imidazoline hydrochloride, prior to exploration and removal of a benign pheochromocytoma.

Newer variants of the alkaloids of ergot are becoming available, largely due to Rothlin (88) of Basle. They are being supplemented by synthetic derivatives of lysergic acid, pending a practical synthesis of lysergic acid itself. There are six natural alkaloids, each occurring in two isomeric forms. Only one form, however, is readily soluble and of high potency. Therefore, the six important forms may be listed as (*a*) the ergotamine group containing pyruvic acid (ergotamine, ergosine), (*b*) the ergotoxine group containing dimethyl pyruvic acid (ergocristine, ergokryptine, ergocornine, and (*c*) ergobasine, to which ergonovine is related. Stoll (89) has shown that ergotoxine is a molecular complex of three alkaloids, i e., ergocristine, ergocornine and ergokryptine The dihydrogenated derivatives of the several alkaloids are of special interest because they appear to be tolerated better than the natural alkaloids and because they afford a more clear-cut sympatholytic action. The dihydrogenated forms have less effect upon the brain, and they inhibit uterine activity, at least in animals. Moreover, they constrict the peripheral vasculature less than natural forms. With respect to adrenolytic action, the dihydrogenated alkaloids block both excitatory and inhibitory *adrenergic effects*

Among these semisynthetic drugs, D-lysergic acid-D-(1-hydroxybutyl-amide-2), known as "Methergine" and dihydroergotamine, known as DHE 45, appear to have clinical promise. For migranous patients in whom ergotamine tartrate causes nervousness, numbness, or vomiting, Alvarez (90) recommends trial of dihydroergotamine (DHE 45) which is only one-fourth as toxic. The usual dose of this preparation has even been used in pregnancy. That the drug is effective in migraine is evident from the studies of Tillgren (91) who compared ergotamine tartrate (in doses of 0.25 to 0 5 mg.) with dihydroergotamine (in doses of 0 5 to 1 0) Of 17 patients, the former relieved 15 and the latter 14; although the onset of relief from the dihydroergotamine was slower A study of untoward side effects in normal subjects showed that ergotamine tartrate caused flushing, nausea, vomiting, and pain in the calves more often than did the dihydro compound, although flushing of the face was more prominent after DHE. Moreover, the symptoms produced by ergotamine tartrate lasted longer. Probably the untoward effects from DHE would be less annoying after intramuscular *injection.*

Similar conclusions have been reached by Orth (154), by Horton (155), and by Friedman & Wilson (92) The last named treated 36 patients suffer-

ing from undoubted migraine with DHE 45 and obtained excellent relief in 32. The amelioration of symptoms, however, was rather slow, i.e., in from 20 min to 2 hr. There was no serious difficulty either from peripheral vasoconstriction or from uterine contraction. Nausea occurred in 4 cases (11 per cent). Moreover, the beneficial results were repeatable.

Stoll and Hofmann (93) synthesized the oxytocic compound ME 277 (methergine) by condensing isolysergic acid azide with D-2 aminobutanol-1. From the resulting product, by transposition, they obtained D-lysergic acid-D-1 hydroxybutyl amide-2. Combined pharmacological and clinical studies by Kirchhof *et al* (94) have shown that it is quite as active on the uterus as ergonovine. Because the supply of the latter is limited, the availability of synthetic lysergic acid compounds is important. Moreover, on theoretical grounds, it is interesting to have a drug which shows high uterine activity but low sympatholytic effects. In women injected with this preparation, a firm contraction of the uterine fundus can be detected in 30 seconds; and the contracted state is maintained for several hours. Satisfactory clinical results in the third stage of labor have been reported by Roberts (95) and by Gipstein (96).

Among sympatholytic drugs, priscoline (i e, 2-benzyl-4,5-imidazoline hydrochloride) has the advantage that it can be used orally (97). This drug is the strongest depressor of blood pressure among the phenyl-substituted alkyl imidazolines Rogers (98) has reviewed the many reports on this drug. It produces dilatation of the vessels of the skin and mucosae, and especially increases the blood flow through extremities. Mueller (99) showed that it had an adrenolytic effect, and Meier & Meyer (100) found that it also showed blocking of the sympathetic nerve impulses. In Rogers' cases the drug appeared to benefit peripheral vascular disease and visceral pain due to vascular spasm. It can be given intravenously or intramuscularly, but oral dosage (20 to 50 mg. every 2 to 4 hr.) proved useful in ambulatory patients. In two cases of causalgia, benefit was attained. The side-effects (101) are not troublesome in doses of 25 to 50 mg, and no appreciable lowering of arterial pressure occurs at this dosage level. The chief complaints are a chilly or crawling sensation of the skin, accompanied by cutis anserina and mild nausea. Intravenous doses produce a flushing and subjective warmth This drug, formerly called "priscol," has been avoided by many clinicians because of its mixed effects. For example, Yonkman, Hays *et al* (102) found a stimulation of the ileum, apparently by cholinergic action It would appear, however, that in low dosage, conveniently given by mouth to ambulatory patients, this drug acts primarily to dilate the peripheral vascular bed.

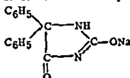
## Central Nervous System Depressants And Antispastic Agents

Slowly a field of neuropharmacology is developing which emphasizes therapeutic effects produced specifically upon different cerebral functions as located in the several functional divisions of the brain. The outstanding advances are in epilepsy and in certain spastic states.

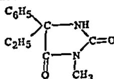
At the present time the nonanesthetic anticonvulsant drugs which can be considered as more than experimental hopes are limited to the bromides, barbiturates, hydantoins, and oxazolidinediones. In grand mal seizures, combinations of phenytoin sodium and phenobarbital or of one of these with Mesantoin (3-methyl-5, 5 phenylethyl hydantoin) give the best results. For petit mal the only well-tried drug is trimethyloxazolidinedione (Tridione). Psychomotor seizures, as pointed out by Merritt (103), are treated less successfully by the grand mal drugs. For phenobarbital its 3-methyl derivative (Mebaral), which has a slightly lower sedative effect, may be used, but at the double-dose required, sedation is about the same. In resistant adult cases it is necessary to push the dosage by combining drugs: e g., by giving three to five times daily a combination of phenytoin sodium (0.1 gm.) with phenobarbital (0.06 gm.), sodium bromide (1.0 gm.) or mesantoin (0.1 gm.). If petit mal attacks occur together with grand mal or psychomotor seizures, tridione should be given, supplemented with phenytoin sodium, phenobarbital, or mesantoin. In status epileptions in adults, Merritt recommends the intravenous injection of about 0.6 gm of sodium phenobarbital or 5 ml. of paraldehyde.

Of the scores of newer antiepileptic drugs, Mesantoin has yielded outstanding results. Aird (104) found, for example, that in convulsive states other than petit mal it is a worthy substitute for phenytoin sodium (Dilantin). In 75 patients for whom the sodium salt of diphenylhydantoin had proved *ineffective or toxic, only eight patients experienced no benefit;* but in seven others toxic symptoms appeared. Of patients with grand mal and Jacksonian seizures alike, 56 per cent were helped greatly, as were 50 per cent of psychomotor seizures. Like most of the recognized antiepileptic drugs, on occasion mesantoin can produce alarming toxic effects. For example, Aird reported one fatal case of aplastic anemia in his series of 75 cases. Other investigators have noted drowsiness, enlarged cervical glands, loss of libido, fever, and skin rashes (105, 106); but these usually can be avoided by initial low dosage, gradually increased. An important procedure is to combine mesantoin with other therapy, so that two drugs may be exployed at once, e g., mesantoin with one of the following: phenobarbital, Mebaral, Delvinal, or Tridione. By such combinations it may be possible to reduce the gingival hypertrophy which is so troublesome in children taking full dosage of Dilantin. Likewise in the treatment of behavior disorders in children this new drug may play a role.

Mesantoin is 3-methyl-5, 5-phenyl-ethyl-hydantoin As shown below, it is closely related to sodium diphenylhydantoinate:




Diphenylhydantoin sodium (Dilantin)




Mesantoin

Experiments with animals (107) indicate that the drug is more effective than Dilantin in raising the convulsive threshold of normal rats to electric shock, and 12 times as safe. Patients with psychomotor seizures may be started on 0.1 gm daily, with a weekly increase by 0.1 gm. for three or four subsequent weeks. Usually 0.4 gm. is an adequate daily dose; but occasionally the dose has been increased to 1.1 gm. daily with benefit. The annoying gastric irritation seen with the sodium salt of diphenylhydantoin is, of course, largely avoided by the use of mesantoin, which can be administered in tablet form. Since Loscalzo's definitive report in 1945 (108), accumulating experience has justified the continued use of this drug. Moreover, as indicated by Fetterman (109), when D-amphetamine sulfate is given concomitantly, drowsiness often is combatted successfully.

Unfortunately these new drugs exhibit annoying or even dangerous side-effects. Shaffer and Morris (132) described severe erythema multiforme of the *pluriorificial* type (Stevens-Johnson syndrome), resulting in blindness in a patient treated with trimethadione (Tridione).

*Synthetic analgetic drugs.*—The appearance of synthetic analgetic drugs, which, despite a relatively simple chemical constitution, rival morphine in potency has raised new problems in the control of addiction. The development of these has been reviewed by Tainter (110) and by van Dyke (111) and stems largely from the discovery by Eisleb and Schaumann in 1939 (112) that their synthetic substitute for atropine was in fact a potent analgetic agent. Meperidine (isonipecaine, Demerol) in doses of 60 to 100 mg. is equally active by mouth and intramuscularly, but the latter route is less erratic. In relation to its analgesia, its atropine-like properties appear trivial. In modern obstetrics and in many preoperative preparations it is proving itself superior to morphine. As compared with morphine it shows less euphoria and sedation, and less respiratory depression, dizziness and nausea Unlike morphine it does not inhibit cough nor retard the activity of the enteric canal. Tolerance develops slowly and is less serious than with morphine Untoward effects include dizziness, dry mouth, nausea, vomiting, flushing, and excessive perspiration. Chemically, meperidine is the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid It has also been called Dolantin and Pethidine

Methadone (Amidon, Miadone, "10820," Dolophine, Adanon) is also of German origin. Chemically it is 6-dimethylamino-4, 4-diphenyl-3-heptanone Studies by Scott, Chen and collaborators (113) indicate that it is twice as potent *as morphine when given by mouth or parenterally Its properties* closely resemble those of morphine, including the characteristic Straub reaction of the mouse's tail It has slight advantages over morphine in its lower likelihood of causing sedation, euphoria, constipation, and respiratory depression. Against cough, in small doses it acts like codeine For the relief of pain it appears to be unexcelled, except that morphine supplies better sedation as preanesthetic medication and meperidine is more suited to obstetrical use.

The drug is only somewhat less addicting than morphine; but the withdrawal symptoms are milder.

Closely allied to dilaudid is metopon, which is its methyl-derived analogue with chemical constitution described as methyldihydromorphinone. Eddy (114) has recommended it for the use of chronic pain in ambulatory patients, especially those with malignant neoplasia. It is highly active after oral administration and twice as potent as morphine. It causes less nausea, vomiting, or sedation than the latter. Because its euphoric effect is less than that of morphine, it is not successful in patients accustomed to poppy. Its likelihood of producing addiction lies intermediate between morphine and the purely synthetic analgetics just described.

Obviously the synthetic drugs offer considerable advantages. They are all, however, subject to Federal regulations under legislation supplementary to the original Harrison Narcotic Act.

*Myanesin.*—The British drug known as "myanesin" (3-o-toloxy-1, 2-propanediol) was originally suggested for use in anesthesia (115). Probably more important, however, is its effect in certain disturbances involving spasm, spasticity, rigidity, and involuntary movements of extrapyramidal origin. As reported by Berger & Schwartz (116) it is effective after oral administration as well as after intravenous use, although the efficacy of the former route is less striking. Observations by Schlesinger and his associates (117, 118) stress the evanescent nature of the response and its failure after small oral doses When an ounce of solution containing 1 gm. of myanesin is administered orally, rapid absorption occurs, unlike the result from tablets. A convenient vehicle is 20 volumes per cent of propylene glycol with 20 volumes per cent syrup of cherry. After about four doses daily for three days, the maximal effect is attained.

In hemiplegic patients, even after a few years, the spasticity due to the exaggerated stretch reflexes may be ameliorated and some recovery of voluntary movement regained. In spastic diplegia, it was observed that without much diminution in spasticity, the physical performance of the patients improved. Improvement was also noted in athetoid and choreiform types of the disease. The nuclei of the brain stem, however, might be so far depressed as to cause decerebrate rigidity. In parkinsonism the results were not dramatic In orthopedic conditions (e g., arthritis of the cervical spine and subacromial bursitis) this drug could relieve painful spasm; this relief doubtless was partly due to an action similar to that of the antipyretic-analgetic drugs like salicylates.

When orally administered, side effects from myanesin are rare except for mild lassitude lasting 10 to 20 min. In severe athetoid crises and in tetanus, treatment in a hospital by intravenous drip may be dramatic when controlled by skilled physicians in attendance Intravenous use, however, may provoke mild muscular inco-ordination, diplopia, and *nystagmus.* Whether chronic toxicity can result after months of therapy is unknown.

In addition Schlan & Unna (119) have reported considerable relief in anxiety states. Myanesin is unexcelled as an antagonist to strychnine. Its cardinal effect is to block internuncial neurones in the central nervous system.

Among the newer drugs under trial for spastic states is "parpanit," the diethylaminoethyl ester of phenyl-cyclopentanecarboxylic acid. This material has a vagolytic effect rather like that of atropine. It also relieves spasm in smooth muscle and stimulates respiration (120). In respect to muscle effects, it antagonizes nicotine, acetylcholine, and diisopropylfluophosphate. Moreover, strychnine convulsions are suppressed. In man, Heuscher & Schoelley (121) found that 12 mg, intravenously injected, induced effects up to 2 hr. These included amblyopia, blushing, tachycardia, irregular breathing, and nausea. Muscular weakness sometimes occurs which responds little to neostigmine (unlike curare). In disorders of the extrapyramidal motor apparatus, the studies of Domenjoz (122) indicate that some benefit may be derived.

*Aids to anesthesia.*—The intravenous administration of procaine, not so long ago limited to local use with a tourniquet in place (123), is now being used by skilled anesthesiologists, e g, Rovenstine & Papper (124) It must be given slowly, by intravenous drip, but it appears not only to combat the cardiac arrhythmias induced by epinephrine and cyclopropane (125) but also to have other effects, e g., analgesia, vasodilatation, antihistaminic action (126), and the relief of muscular spasm Derivatives of procaine are also under trial, such as its metabolite, diethylaminoethanol. The pain threshold rises by about one-third, and the effect is particularly good in fractures where associated muscle-spasm complicates the lesion (127) The drug is so given (in expert hands) that it continuously causes mild toxicity; e g., metallic taste, vertigo, nausea, and warmth Obviously, the dosage must be insufficient to produce tremors, delirium, and convulsions Whereas in the treatment of anesthetized patients with cardiac arrhythmia a rapid injection of 100 ml. of 1 per cent solution is used, Graubard suggests that in the unanesthetized patient 4 mg per kg. of body weight be infused over the course of 20 min as a 0.1 per cent solution in isotonic saline Vitamin C and barbiturates are frequently used concurrently as a safety measure. In serum sickness and in the spastic stage of poliomyelitis, in burns, severe pruritis, and giant urticaria the drug appears to have merit.

The use of D-tubocurarine in anesthesia is already so well established that it will not be discussed here As pointed out by Harvey (128) the great contribution to surgery resulting from the application of sulfuric ether in 1846 was relaxation rather than analgesia. Indeed Cullen (129) has demonstrated the peripheral curariform action of ether, or at least its synergism with curare. Major operations have even been performed with curare alone as the major anesthetic (130); and although this practice is not to be recommended on psychic grounds, the surgical results were excellent. Apparently the relief of pain possibly may be a humane luxury, when viewed in cold-blooded objectivity, provided that the surgeon has a relaxed patient. At

least, such theoretical considerations indicate that future progress may lie in drugs designed to relieve spasm. For instance, D-tubocurarine has been employed by Norcross *et al.* (131) in rheumatoid spondylitis.

Lennox and others have reported preliminary results with two newer antiepileptic drugs, i.e., "phenurone" and "paradione." At this time it is too early to appraise these compounds

## Diuretics

As described by Gold *et al.* (133), cardiologists and internists are laying greater emphasis upon the use of diuretics and sodium-poor diets in the treatment of chronic heart disease. This is true whether digitalis leaf or the purified glycosides (digoxin, digitoxin or Lanatoside C) are used, as compared by Batterman & DeGraff (134). In the use of mercurial diuretics in such therapeutic regimens, the hazard of ventricular fibrillation following intravenous injection has restricted their free use (135, 136). Lehman & DeGraff (137) have found recently that if theophylline is replaced by a sulfhydryl group in the classical mercurial, the danger of ventricular fibrillation after intravenous injection practically disappears. Moreover, the local reaction at the site of injection (even subcutaneously) is insignificant if edematous areas, poorly supplied with circulation, be avoided.

The new product, known as Thiomerin commercially, is the disodium salt of N(γ-carboxymethylmercapto-mercuri-β-methoxy) propyl camphoramic acid, with the following structure:




It is a white amorphous powder, readily soluble in water. Obviously it is identical with mercurophylline (U.S.P. XIII) except that, instead of theophylline, it contains sodium mercapto-acetate in chemical combination with the mercury. Each ml. of the preparation contains 39 mg. of mercury. Subcutaneous dosage ranges from 0 5 to 2.0 ml. Studies of its local toxic action on tissue by Lehman, Taube & King (138) show that it fails to produce the cutaneous necrosis caused by the subcutaneous injection of Mercuzanthin or Mercuhydrin. After intramuscular injection all three drugs cause a polymorphonuclear exudate, but the "Thiomerin" exudate regresses, whereas the other two drugs cause fibrosis. When tested for immediate cardiac toxicity in the cat (by electrocardiogram), this new drug is tolerated in dosage up to 160 times that of Mercuhydrin. Mercuzanthin, Salyrgan-theophylline and mercuric chloride were even more toxic in the order given (139). As judged by widening of the QRS interval after intravenous injection these values are striking when mercuric chloride is given a score of 1.0. Corresponding values were: for Salyrgan-theophylline 1 4; for Mercuzanthin 1.8; for mercuhydrin 2.5; for Thiomerin 400+.

It should be emphasized that the late lethal dosage of these several

organic diuretics is much the same. Likewise, their absorption from an intramuscular depot is similar. In clinical comparisons (140) of these three organic mercurials, no significant differences in diuretic effects were noted except for the transient hemodynamic response to the theophylline fraction of Mercuzanthin. The action of all three compounds on renal tubules is similar. The application of this new diuretic drug in clinical myocardial insufficiency has been discussed by Herrmann (141), who used the drug intravenously in 20 cardiac patients and subcutaneously in 135 patients, with adequate response observed.

### ANTIHYPERTENSION SUBSTANCES

The problem of essential hypertension we have always with us One drug after another is tried with disappointing results. Hope springs eternal, however, and a recent study by Wilkins, Freis & Stanton (142) is of interest. It deals with two drugs which seemed helpful, namely veratrum viride and dihydroergocornine Of course, monkshood and ergot are old acquaintances, but modern methodology may implement their action Both are effective by mouth and can be used over prolonged periods. Veratrum may easily lead to nausea, vomiting and collapse and, therefore, should be reserved for patients whose hypertension is severe. One modern preparation available is known as Vertanis. In cases of encephalopathy, with or without myocardial failure, due to hypertension, acute hypotension may be dramatic (143) after its use. Measurements of blood flow in the forearm and calf, and in the kidney, and observations on the retina (144) all indicate that a generalized decrease in peripheral resistance occurs. After the parenteral use of veratrum viride as Veratron, oliguria may ensue temporarily. The mechanism of veratrum action on blood vessels appears to be neither sympatholytic nor parasympathomimetic, yet nervous action appears to be involved Because the action is sometimes heroic, the dosage should be adjusted to the individual patient.

Less drastic is dihydroergocornine (DHO 180), but less effective. It also is capable of lowering the arterial pressure of certain hypertensive patients without reducing (except initially) the cardiac output or the blood flow through the kidneys, liver, or extremities, when measured in the horizontal position. Fewer patients respond to the drug, however, and these tend to become tolerant to it. Moreover, (unlike veratrum) it causes postural hypotonus, similarly to TEAC, as already described in an earlier section. Unlike TEAC, however, it seldom produces tachycardia, but rather bradycardia. The hypotensive effect varies greatly among patients. It is assumed that both of these drugs act through the central nervous system—a feature which would differentiate them from nitrites, dibenamine, or TEAC. Accordingly these drugs maintain the patient in a state of circulatory equilibrium, but at a lower arterial pressure.

Norepinephrine (arterenol, sympathin N) may come into general use in

place of epinephrine. Indeed, natural epinephrine, as pointed out by Tainter (145), may contain over 20 per cent of arterenol. The levorotatory norepinephrine has only excitor action on blood vessels (146), whereas epinephrine has vasodilator properties in low concentrations. The increase in blood pressure after epinephrine is due largely to increased cardiac output; whereas that which follows arterenol occurs from widespread vasoconstriction with little change in stroke volume. With arterenol pressor responses can be obtained in patients suffering from acute hemorrhagic shock which is not relieved by blood transfusion alone. It is also of value in hypertensive patients subjected to thoracolumbar sympathectomy.

## Acute Renal Failure

Largely through the work of Kolff (147), conducted in Holland under great difficulties, interest has revived in vividialysis and related procedures in acute renal failure The management of acute renal failure, according to Snapper (148), is designed to tide the patient over an acute phase until spontaneous healing can occur. Acute glomerulonephritis tends toward healing; and after nephrotic degeneration of the lower nephron, regeneration of the tubules always starts in 10 days. During the period of acute anuria, Snapper suggests that the intake of fluids, electrolytes, and proteins be reduced In the absence of diarrhea, a daily diet of 800 ml. of fruit juice will suffice for several days. Later fat and carbohydrate must be added. For acidosis sodium bicarbonate should be given; for hypochloremia, sodium chloride.

Large quantities of water and salt should be avoided, because they worsen the patient's status and necessitate more drastic measures These "drastic" measures include the artificial kidney, peritoneal dialysis, intestinal irrigation and exsanguinotransfusion Snapper has reported 11 uremic cases probably saved by the artificial kidney and 21 by peritoneal dialysis. He concludes that the present techniques for intestinal irrigation are unsatisfactory, especially because dangerous changes in the blood electrolytes are likely to follow. All methods require the co-operation of skilled personnel.

Replacement transfusion (149) has the disadvantages that heparinization is necessary and that large quantities of blood are needed. Unless the type is rare, however, it can be repeated often, and the chief accidents due to irregular agglutinins can be avoided by suitable precautions The procedure withdraws all toxic products, including the non-dialysable myohemoglobin, and establishes the composition of the normal bloody fluids

Intraperitoneal dialysis (150, 151) yields a urea clearance of 11 ml of blood per min. when the inflow of dialyzing fluid into the peritoneum is at the rate of 1 l. per hr. Thus peritoneal dialysis, on the average, can attain well over half the clearing capacity of the kidneys; but it rarely can be continued over five days and, due to adhesions, usually cannot be repeated. Obviously this procedure withdraws only crystalloids, including both desir-

able and undesirable metabolites without discrimination. In addition, there is a definite hazard of plastic peritonitis or peritoneal infection with septicemia from *Bacillus perfringens* and other organisms

Intestinal irrigation has been tried in man, both of the colon and of the small intestine. For example, Kolff (152) irrigated the colon through an appendicostomy. Oppenheimer & Rosenak (153) used a modified Miller-Abbot tube, inserted through the nose, to reach the middle portion of the small intestine. In less than two days the blood urea nitrogen was reduced from 90 to 46 mg. per cent. On the whole, however, intestinal irrigation has not proved satisfactory.

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# ANNOTATED LIST OF REVIEWS IN MEDICINE

By E. M. MacKay

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The following list includes reviews published between July, 1948 and November, 1949. About half of them were read in their entirety, and the remainder were carefully perused. Some reviews which appeared during the period under consideration but were unavailable for examination will be listed in the next volume.

Notes have been made about the reviews in regard to whether they are clinical or of a more basic nature. The question of a review being a summary of the literature or of a subject is considered. Whether an article is of a critical nature or a simple summary may also be important.

## Infectious Diseases

1. "Progress in Internal Medicine; Infectious Diseases," Reimann, H. A., *Arch. Internal Med.*, 82, 468–516 (1948), 226 references. A yearly summary of the literature.

2. "Primary Atypical Pneumonia and Influenza (Diagnosis, Prevention and Treatment)," Horsfall, F. L., Jr., *Bull. N. Y. Acad. Med.* 24, 431–46 (1948), 35 references. A detailed summary of the subject presented in a useful and practical manner.

3. "Medical Progress—Tuberculosis," Wassersug, J. D., *New Engl. J. Med.*, 240, 463–72 (1949), 55 references. A summary of therapy stressing newer developments.

4. "BCG and the Newer Epidemiology of Tuberculosis," Birkhaug, K., *Bull. N. Y. Acad. Med.*, 24, 409–30 (1948), 51 references. A brief summary of the present status of the subject.

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7. "Medical Progress—Rubella (German Measles) and Congenital Deformities," Wesselhoeft, C., *New England J. Med.*, 240, 258–61 (1949), 18 references. A critical clinical review of current information.

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9. "The Etiology of Rheumatic Fever: A Review of Theories and

Evidence," WAKSMAN, B. H., *Medicine*, 28, 143–200 (1949), 707 references A concise summary of the extensive literature on the subject.

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11. "Combined Immunizations," LAPIN, J. H., *Advances in Pediat*, 4, 145–230 (Interscience Publishers, Inc., New York, 1949), 256 references. A complete and critical summary of interest to the immunologist as well as the pediatrician.

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13. "Medical Progress—Active Immunization," EDSALL, G., *New Engl. J. Med*, 241, 18–26, 60–70 (1949), 309 references. An extensive review of the literature.

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20. "Viral Hepatitis," STOKES, J., JR., *Advances in Pediat*, 3, 131–57 (Interscience Publishers, Inc., New York, 1948) 72 references. A brief clinical summary.

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10. "Recent Advances in Surgery—Hemorrhage into the Biliary Tract Following Trauma—'Traumatic Hemobilia,'" SANDBLOM, P., *Surgery*, 24, 571–86 (1948), 35 references. A review of personal experience in the field.

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6. "The Collateral Circulation Following Ligation of the Inferior Vena Cava," ROBINSON, L S., *Surgery*, 25, 329–47 (1949), 107 references. An original study accompanied by an excellent review of the literature and the subject.

7. "Recent Advances in Surgery—Lumbar Sympathectomy for Arteriosclerosis Obliterans," BLAIN A., 3RD AND CAMPBELL, K. N., *Surgery*, 25, 950–62 (1949), 28 references A critical discussion of a controversial subject.

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2. "Management of Acute Renal Failure," SNAPPER, I, *Bull. N. Y. Acad. Med.*, **25**, 199–227 (1949), 49 references. In part a review of the literature and in part a summary of the author's experience.

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3. "Current Concepts of Hemolytic Anemias," ESTREN, S, AND DAMESHEK, W., *Advances in Internal Med.* **3**, 45–104 (Interscience Publishers, Inc., New York, 1949), 198 references The subject as well as the recent literature are both surveyed in detail.

4. "The Present Status of Vitamin $B_{12}$ in Pernicious Anemia," REISNER, E. H, JR., *Bull N. Y. Acad. Med.*, **25**, 429–33 (1949), 22 references. A very brief review.

5. "Hematopoiesis," CARTWRIGHT, G. E, AND WINTROBE, M. M, *Ann. Rev. Physiol*, **11**, 335–54 (1949), 194 references A review of the recent literature dealing with the physiology of the blood and its clinical implications.

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7. "Medical Progress: Rh and Other Blood Groups," DIAMOND, L. K., AND ALLEN, F. H., JR., *New Engl. J. Med.*, 241, 867–73 (1949), 33 references. A splendid up to date review.

8. "Progress in Pediatrics—Normal and Pathologic Physiology of the Bone Marrow," ZUELZER, W. W., *Am. J. Diseases Children*, 77, 482–502 (1949), 2 references. A personal review of the subject. No literature.

9. "Iron Metabolism and Hemochromatosis," GRANICK, S., *Bull. N. Y. Acad. Med.*, 25, 403–28 (1949), 43 references. An excellent review which organizes the subject as well as reviewing the literature.

10. "The Use of Radioactive Isotopes in the Study of Iron and Hemoglobin Metabolism and the Physiology of the Erythrocyte," HAHN, P. F., *Advances in Biol. Med. Physics*, 1, 287–319 (Academic Press, Inc., New York, 1948), 62 references. A literature summary for the investigator.

11. "The Reticulo-endothelioses in Children," SIWE, S., *Advances in Pediat.*, 4, 117–43 (Interscience Publishers, Inc., New York, 1949), 81 references A careful review of the medical and pathological literature of the subject. German reports are particularly well covered.

12. "Medical Progress—Methemoglobinemia and Sulfhemoglobinemia," FINCH, C. A., *New Engl J. Med.*, 239, 470–78 (1948), 142 references. A practical review of interest to the clinician and the investigator.

13. "Medical Progress—Blood and its Derivatives," GIBSON, S. T., *New Engl J. Med.*, 239, 544–56, 579–89 (1948), 381 references Blood storage, blood fractions and substitutes are dealt with in detail. Therapeutic uses are reviewed.

14. "Plasma Fractionation," JANEWAY, C. A., *Advances in Internal Med.*, 3, 295–372 (Interscience Publishers, Inc., New York, 1949), 196 references. The literature is covered from the point of view of immunology and this therapeutic use of plasma fractions as well as their use in shock.

15. "The Lymphatic System," WHITE, A., *Ann. Rev. Physiol.*, 11, 355–86 (1949), 201 references. The literature on the normal and pathological physiology of the lymphatic system is critically reviewed for the years 1945 to 1948

## NUTRITION AND NUTRITIONAL DISEASES

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2. "Synthesis of Lipides," KLEINZELLER, A., *Advances in Enzymol.*, 8, 299–341 (Interscience Publishers, Inc., New York, 1948), 151 references. A specialized summary of some interest to the nutrition specialist.

3. "Medical Progress Vitamin Supplementation in Health and Disease," CULVER, P. J, *New Engl J. Med.*, 241, 970–77, 1011–17, 1050–57 (1949), 247 references. An excellent critical consideration of an important subject. Practically all of the pertinent literature is covered.

4. "Clinical Aspects of Vitamins," SPIES, T. D., *Ann. Rev. Biochem.*, **17**, 449–70 (1948), 47 references. A review which covers the clinical side of the newer vitamin knowledge.

5. "The Vitamins," OSER, B. L., *Ann. Rev. Biochem*, **17**, 381–448 (1948), 372 references. A thorough review of the experimental literature over the preceding year.

6. "Progress in Pediatrics—Plasma Vitamin A and Its Clinical Significance, A Review," ARON, H. C. S., *Am. J. Diseases Children*, **77**, 763–73 (1949), 25 references A critical review with a clinical slant covering recent years.

7. "Vitamin P." SCARBOROUGH, H., AND BACHARACH, A. L, *Vitamins & Hormones*, **7**, 1–55 (Academic Press, Inc., New York, 1949), 205 references. A critical summary of the subject covering all aspects of the problem.

8. "The Chemistry and Biological Action of Pteroylglutamic Acid and Related Compounds," HUTCHINGS, B L, AND MOWAT, J. H, *Vitamins & Hormones*, **6**, 1–22 (Academic Press, Inc, New York, 1948), 72 references, Designed for the specialized investigator.

9. "Vitamin K," DAM, H, *Vitamins & Hormones*, **6**, 27–48 (Academic Press, Inc., New York, 1948), 206 references. This review deals with all vitamin K developments since 1941.

10. "The Physiology of Thiamine," JANSEN, B. C. P, *Vitamins & Hormones*, **7**, 83–110 (Academic Press, Inc., New York, 1949), 166 references A highly technical review for the investigators

11. "Diet and Aging," MCCAY, C. M, *Vitamins & Hormones*, **7**, 147–70 (Academic Press, Inc., New York, 1949), 67 references. Careful summary of all aspects of the subject and literature

12. "The Relation of Nutritional Deficiencies to Graying," FROST, D. V., *Physiol. Revs*, **28**, 368–82 (1948), 107 references. A nonclinical review of fundamental work.

13. "Clinical Features and Pathogenesis of Tropical Sprue," STEFANINI, M., *Medicine*, **27**, 379–427 (1948), 123 references A summary of war time observations

14. "New Advances in Gout," ADLERSBERG, D, *Bull. N. Y. Acad. Med*, **25**, 651–65 (1949), 48 references A brief clinical review of the present status of our knowledge of gout.

15. "Cystinosis· Cystine Disease (Lignac's Disease) in Children," FREUDENBERG, E., *Advances in Pediat.*, **4**, 265–92 (Interscience Publishers, Inc., New York, 1949), 46 references A complete clinical summary of the condition

16. "Lipid Metabolism," CHAIKOFF, I L, AND ENTENMAN, C., *Ann. Rev. Biochem*, **17**, 253–74 (1948), 123 references. The preceding year's literature reviewed for the investigator.

17. "The Metabolism of Proteins and Amino Acids," ALLISON, J. B., *Ann. Rev. Biochem.*, **17**, 275–302 (1948), 190 references The recent literature summarized for the metabolism chemist.

18. "Carbohydrate Metabolism," VENNESLAND, B., *Ann. Rev. Biochem.*, 17, 227–52 (1948), 258 references. Complete coverage of the preceding years' literature for the biochemist and metabolic expert.

19. "The Physiological Basis of Voluntary Food Intake (Appetite?)," LEPKOVSKY, S., *Advances in Food Research*, 1, 105–48 (Academic Press, Inc., New York, 1948), 160 references. An excellent provocative review of a long neglected subject. Although of necessity largely based on experimental work, there are numerous clinical implications.

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1. "Iodine Metabolism," LEBLOND, C. P., *Advances in Biol. Med. Physics*, 1, 353–86 (Academic Press, Inc., New York, 1948), 150 references. An excellent review of basic work

2. "Physiologic Reactions of the Thyroid Stimulating Hormone," RAWSON, R. W., AND MONEY, W. L., *Recent Progress in Hormone Research*, 4, 397–428 (Academic Press, Inc., New York, 1949), 58 references. A careful summary of the authors' contributions.

3. "The Metabolism of Iodine in Man as Disclosed with the Use of Radioiodine," KEATING, F. R., JR., AND ALBERT, A, *Recent Progress in Hormone Research*, 4, 429–81 (Academic Press, Inc., New York, 1949), 37 references. A detailed review of the subject and literature primarily of clinical interest

4. "Radioiodine as a Diagnostic and Therapeutic Tool in Clinical Medicine," SEIDLIN, S. M , *Recent Progress in Hormone Research* 4, 483–510 (Academic Press, Inc., New York, 1949), 11 references A review of the author's contributions.

5. "The Clinical Use of Radioactive Iodine," WERNER, S. C., QUIMBY, E. H., AND SCHMIDT, C., *Bull. N. Y. Acad. Med.*, 24, 547–60 (1948), 6 references. A brief review through 1948.

6. "Treatment of Hyperthyroidism with Antithyroid Compounds," ASTWOOD, E B , *Advances in Internal Med* , 3, 237–74 (Interscience Publishers, Inc., New York, 1949), 67 references Summarizes the available information on the use of antithyroid compounds but does not assess their relative merits

7. "Biochemistry of the Hormones—Thyroid," GALLAGHER, T. F., *Ann. Rev Biochem.*, 17, 349–80 (1948), 201 references. Current literature reviewed

8. "Exophthalomos," BRUNTON, C., *Physiol. Revs.*, 29, 260–80 (1949), 141 references An excellent review of a subject which has perplexed many observers.

9. "The Actions of the Hormones of the Posterior Lobe of the Pituitary Gland upon the Circulation and the Secretion of Urine," STEHLE, R. L., *Vitamins & Hormones*, 7, 389–435 (Academic Press, Inc., New York, 1949), 250 references A thorough review of a subject of interest to clinical investigators, obstetricians, and internists, and others.

10. "The Chemistry of the Hormones of the Posterior Lobe of the Pitui-

tary Gland," STEHLE, R L, *Vitamins & Hormones*, 7, 383–88 (Academic Press, Inc., New York, 1949), 25 references. A brief summary of an unexplored field.

11. "Effects of Hypothalamic Lesions on Water and Energy Metabolism in the Rat," STEVENSON, J. A. F., *Recent Progress in Hormone Research*, 4, 363–94 (Academic Press, Inc., New York, 1949), 79 references. Critical summary of an experimental field with a bearing on medicine.

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15 "The Alarm Reaction and the Diseases of Adaptation," SELYE, H., *Ann. Internal Med*, 29, 403–15 (1948), 41 references A good summary of the author's well known theory.

16. "The Influence of the Adrenal Cortex on the Metabolism or Water and Electrolytes," KENDALL, E C, *Vitamins & Hormones*, 6, 277–321 (Academic Press, Inc., New York, 1948), 256 references. An unusually complete study of the literature applying to all phases of the problem

17. "Nature and Significance of Neutral Steroids in Human Urine in Normal and in Abnormal States· With a Preliminary Consideration of the Adrenal and Gonadal Steroids and the Factors which Influence Their Secretion and Biological Action," ENGSTROM, W W, *Yale J Biol and Med*, 21, 21–85 (1948–49), 250 references An excellent review on a specialized topic. Well documented with summarized data from the literature.

18. "Alloxan Diabetes," LUKENS, F. D. W, *Physiol Revs*, 28, 304–30 (1948), 172 references An interesting subject is summarized with the inclusion of recent literature.

19 "Alloxan Diabetes," BAILEY, C C., *Vitamins & Hormones*, 7, 365–82 (Academic Press, Inc, New York, 1949), 76 references The status of this interesting type of diabetes is brought up to date.

20. "Factors controlling the Development and Progression of of Diabetes," LAZAROW, A., *Physiol Revs*, 29, 48–74 (1949), 168 references. Considers the literature covering the subject for both experimental and human diabetes.

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7. "Testis Tumors," LEWIS, L. G., *Advances in Surg*, 2, 419–94 (Interscience Publishers, Inc., New York, 1949), 144 references Reviews the subject thoroughly as well as covering the literature.

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9. "Abnormalities and Variations of Sexual Development during Childhood and Adolescence," WILKINS, L, *Advances in Pediat.*, 3, 159–217 (Interscience Publishers, Inc., New York, 1948), 195 references. A complete review of the current status of this subject.

10. "Hormones and the Differentiation of Sex." BURNS, R. K., *Biol Progress*, 1, 233–66 (Academic Press, Inc., New York, 1949), 23 references An excellent survey of the present status of the fundamental knowledge in the field

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3. "Modern Therapeutic Agents Used in Neurologic Conditions," MERRITT, H H., *Advances in Internal Med*, 3, 395–444 (Interscience Publishers, Inc., New York, 1949), 27 references. A detailed summary including doses, methods of administration and choice of agents

4 "The Use of Antiepileptic Drugs," MERRITT, H H, *Bull. N. Y. Acad. Med.*, 25, 5–15 (1949), 22 references A detailed summary of the current use of drugs for therapy in epileptics

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9 "The Landry-Guillain-Barre Syndrome," HAYMAKER, W., AND

Kernohan, J. W., *Medicine*, 28, 59–141 (1949), 225 references A review of the literature augmented by a study of many new cases.

10. "Recent Advances in Surgery—An Analysis of the Treatment of Trophic Ulcers," Goldfarb, A., and Wagner M., *Surgery*, 24, 744–54 (1948), no references. A review of the subject from the authors' experience.

11. "Treatment of Bell's and Other Palsies," Bierman, W, *Bull. N. Y Acad Med.*, 25, 307–22 (1949), 31 references Brief outline of the practical details of therapy.

12 "Subdural Hematoma in Infancy," Ingraham, F. D., and Matson, D. D., *Advances in Pediat*, 4, 231–63 (Interscience Publishers, Inc., New York, 1949), 17 references. A detailed summary of the authors' experience.

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14. "Motion Sickness," Tyler, D. B., and Bard, P., *Physiol Revs.*, 29, 311–69 (1949), 237 references. A complete and critical summary containing something for anyone interested in the subject.

15. "Medial Progress—Neurophysiology, 1942–1948," Fulton, J. F., *New Engl J Med*, 240, 883–91, 920–27 (1949), 102 references A superb review of the field.

16 "Visceral Functions of the Nervous System," Youmans, W. B, *Ann. Rev. Physiol.*, 11, 139–60 (1949), 123 references. Recent work through mid 1948 is well summarized.

17. "Somatic Functions of the Nervous System," Magoun. H. W., *Ann. Rev Physiol*, 11, 161–72 (1949), 85 references. The recent literature up to July 1948 is well reviewed.

18 "Bioelectric Potentials in the Nervous System and Muscle," Lloyd, D. P. C, and McIntyre, A K, *Ann. Rev. Physiol.*, 11, 173–98 (1949), 102 references Reviews the literature for the year ending in June 1948.

19. "The Electrical Activity of the Brain," Walter, W G., and Walter V. J, *Ann. Rev Physiol*, 11, 199–230 (1949), 266 references. Reviews the literature for the year prior to June 1948.

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4. "Physiological Psychology," Harlow, H F., *Ann. Rev. Physiol.*, 11,

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5. "The Present Status of Clinical Electroencephalography," GIBBS, F. A., *Bull. N. Y. Acad. Med.*, **25**, 764-74 (1949), 27 references. A brief clinical summary.

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12. "Emotions and Symptoms in Pediatric Practice," SENN, M. J. E., *Advances in Pediat*, **3**, 69-89 (Interscience Publishers, Inc., New York, 1948), 17 references. An interesting summary of ideas and opinions.

### DISEASES OF THE BONES AND JOINTS

1. "Medical Progress—Surgery in Chronic Arthritis," KUHNS, J. G., *New Engl. J Med.*, **240**, 605-10 (1949), 86 references A careful critical review covering all phases of the problem

2. "The Osteochondroses," HOWORTH, B, *Advances in Pediat.*, **3**, 297-342 (Interscience Publishers, Inc., New York, 1948), no references A detailed personal review of the subject without documentation.

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1 "Progress in Internal Medicine; Review of Neuropsychiatry for 1948," COBB, S, *Arch. Internal Med.*, 83, 454–69 (1949), 43 references. Complete coverage of the literature

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4. "Genetic Effects of Radiations," CATCHESIDE, D G., *Advances in Genetics*, 2, 271–358 (Academic Press, Inc., New York, 1948), 381 references. An extensive review of the more recent literature dealing with fundamental experimental work.

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6. "The Effects of the Atomic Bomb on the Japanese," HOWLAND, J. W., AND WARREN, S. L., *Advances in Biol. and Med. Physics*, 1, 387–408 (Academic Press, Inc., New York, 1948), no references. Reviews as much information as has been released.

7. "Medical Progress—X-Ray Diagnosis of Pulmonary Lesions," ROBBINS, L. L., *New Engl. J. Med*, 239, 779–86 (1948), 130 references. A useful clinical summary.

### DISEASES OF THE EYE, NOSE AND THROAT

1. "Vision," TALBOT, S. A., *Ann. Rev. Physiol.*, 11, 245–68 (1949), 288 references. A survey of the year's literature through mid 1948.

2 "Hearing," WALZL, E. M , *Ann. Rev. Physiol.*, 11, 231–44 (1949), 52 references. A review of the literature for a year before June 1948.

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4. "Retrolental Fibroplasia," TERRY, T. L., *Advances in Pediat*, 3, 55–67 (Interscience Publishers, Inc , New York, 1948), 35 references. The literature and subject matter of a rare condition are well covered

### LABORATORY AIDS TO DIAGNOSIS AND THERAPY

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2. "The Present Status of Liver Function Tests Including Observations on the Newer Flocculation Procedures," BRUGER, M , AND OPPENHEIM, E , *Bull. N Y Acad Med*, 25, 16–31 (1949), 52 references A brief unique organization and comparison of current liver function tests

3. "Some Observations on Liver Function Tests," KLATSKIN, G., *Yale J. Biol. Med*, 21, 127–43 (1948–49), 46 references A reasonably complete summary of all such tests and their significance.

4. "Medical Progress—Pregnancy Tests," ROBBINS, S. L , *New Engl. J. Med*, 239, 333–39, 369–73 (1948), 99 references A most useful outline of the methods, their mechanism, and interpretation

2. "Medical Progress: Resuscitation," Wiggin, S. C, Saunders, P., and Small, G. A., *New Engl. J. Med*, 241, 413–20 (1949), 223 references. An excellent and detailed review of the subject as well as the literature.

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5. "Pulmonary Insufficiency," Baldwin, E. DeF., Cournand, A., and Richards, D. W., Jr., *Medicine*, 27, 243–78 (1948), 59 references. A review of methods of measurement and of classification.

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7. "Pulmonary Insufficiency," Baldwin, E. DeF., Cournand, A., and Richards, D. W., Jr., *Medicine*, 28, 201–37 (1949), 16 references. A review of the pulmonary insufficiency due to chronic pulmonary emphysema based on the authors' experience.

8 "Medical Progress—Thoracic Surgery," Scannell, J. G, *New Engl J. Med.*, 239, 924–31, 961–72 (1948), 165 references. A critical review of the recent literature.

9. "Pulmonary Function Studies in Relation to Chest Surgery," Riley, R L., and Cournand, A F., *Advances in Surg*, 2, 1–39 (Interscience Publishers, Inc., New York, 1949), 31 references. A personal summary of the point.

10. "Modern Treatment of Pulmonary Suppuration," Andrus, W. DeW., *Bull. N. Y Acad. Med.*, 24, 481–90 (1948), 9 references. A short general review.

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2. "Development of Acute Tissue Damage Due to Cold," Kreyberg, L., *Physiol. Revs.*, 29, 156–67 (1949), 45 references. A brief summary of work on the subject reported during and after the war.

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2. "Health Physics, Instrumentation and Radiation Protection," Parker, H. M., *Advances in Biol Med Physics*, 1, 223–85 (Academic Press, Inc., New York, 1948), 104 references. A summary of interest to all workers in radiation or who handle radioactive materials

D. M., *Quart. J. Med*, 41, 271–90 (1948), 115 references. A good review to the date of preparation.

9. "Vitamins as Pharmacologic Agents," MOLITOR, H., AND EMERSON, G. A, *Vitamins & Hormones* 6, 69–93 (Academic Press, Inc., New York, 1948) 282 references. An authoritative summary with such clinical applications as exist.

10. "The Major Toxic Actions of Insecticides, LEHMAN, A. J., *Bull. N. Y. Acad. Med*, 25, 382–87 (1949), no references. An interesting summary of the action of the newer agents which as yet are represented by few reports in the literature.

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